Thyroid – Goals and Objectives

- Define and discuss the following terms:
  - Thyrotoxicosis: hyperthyroidism
  - Hypothyroidism
  - Hashimoto’s thyroiditis
  - Riedel’s thyroiditis
  - Graves’ disease: Graves’ disease
  - Cretinism: Goiter
  - DeQuervain’s thyroiditis
  - Lymphocytic thyroiditis

- Compare and contrast the etiology-pathogenesis and clinical manifestations of hyperthyroidism and hypothyroidism. Differentiate between primary and secondary hypothyroidism.

- Compare and contrast the characteristic features of Hashimoto’s thyroiditis, subacute granulomatous thyroiditis, and subacute lymphocytic thyroiditis.

- Describe the pathogenesis, epidemiology, pathology, and clinical manifestations of Graves disease.

- Compare and contrast the characteristic features of diffuse (simple) and multinodular goiter.

- Briefly describe the embryologic derivation and pathology of a thyroglossal duct cyst.

Reading Assignment: Robbins Pathologic Basis of Disease (Cotran, Kumar, Robbins), 10th Ed. Chapter 20, pp. 755-768

Thyroid Gland

- Right lobe
- Isthmus
- Thyroid follicles
- Thyroid gland
Normal histology of the thyroid gland

- Gland is divided into lobules by thin fibrous septae
- Each lobule has 20 to 40 evenly distributed follicles
- Each follicle is lined by cuboidal to low columnar follicular cells
- Follicles also contain parafollicular or "C" cells which secrete calcitonin
- Calcitonin promotes absorption of calcium by the skeletal system and inhibits resorption of bone by osteoclasts

Mechanism of action and function of thyroid hormones

- Stimulation of protein synthesis
- Up regulation of carbohydrates and lipid catabolism
- Increase in basal metabolic rate
- Critical role in the development of brain in fetuses and neonates

Diseases of the Thyroid

- Excessive release of the thyroid hormones (hyperthyroidism)
- Thyroid hormone deficiency (hypothyroidism)
- Tumors
Thyrotoxicosis

- Hyper metabolic state due to increased circulating levels of thyroid hormones (T4 and T3)
- Most commonly caused by hyper functioning of the thyroid gland, hence often the term hyperthyroidism is used interchangeably with thyrotoxicosis
- Thyrotoxicosis may be caused by disorders not associated with hyperthyroidism as highlighted in the table on next slide

Disorders associated with thyrotoxicosis

(1g 756 table 20-2)

- ASSOCIATED WITH HYPERTHYROIDISM
  - Primary
    - Diffuse toxic hyperplasia (Grave’s Disease)
    - Hyperfunctioning (toxic) multinodular goiter
    - Hyperfunctioning (toxic) adenoma
    - Neonatal thyrotoxicosis associated with maternal Graves disease
  - Secondary
    - TSH secreting pituitary adenoma (rare)

- NOT ASSOCIATED WITH HYPERTHYROIDISM
  - Granulomatous (de Quervain) thyroiditis (painful)
  - Subacute lymphocytic thyroiditis (painless)
  - Struma ovari (ovarian teratoma with ectopic thyroid)
  - Factitious thyrotoxicosis (exogenous thyroid intake)

Hyperthyroidism / Thyrotoxicosis

Clinical Manifestations

- Clinical features are due to hypermetabolic state due to excess of thyroid hormones and over activity of sympathetic nervous system
- Constitutional symptoms: soft warm flushed skin, heat intolerance and excess sweating, characteristic weight loss despite increased appetite
- Cardiovascular - palpitations and tachycardia, development of congestive heart failure in elderly as a consequence of pre existing heart disease
- Neuromuscular: nervousness, tremor and irritability, proximal muscle weakness and decreased muscle mass – thyroid myopathy
Hyperthyroidism / Thyrotoxicosis

Clinical Manifestations

- Gastrointestinal: hypermotility, malabsorption and diarrhea
- Ocular: wide staring gaze and lid lag (sympathetic overstimulation of levator palpebrae superioris)
- Thyroid ophthalmopathy (proptosis) only associated with Graves
- Thyroid storm – medical emergency – abrupt onset of hyperthyroidism, most commonly seen in patients with history of Graves disease during infection, surgery, cessation of antithyroid medication or stress
- Apathetic hyperthyroidism: thyrotoxicosis in elderly where typical clinical features not seen

Diagnosis of hyperthyroidism

- Measurement of TSH levels - single most sensitive screening test (usually decreased)
- Free T4 (usually increased)
- T3 toxicosis – rare patients with normal or reduced T4 but elevated T3
- In rare cases of secondary or pituitary associated hyperthyroidism TSH levels may be normal or raised
- Radioactive iodine uptake – after diagnosis of thyrotoxicosis; diffuse uptake (Graves), localized (toxic adenoma), reduced uptake (thyroiditis)
Hypothyroidism

• Hypometabolic state secondary to inadequate levels of thyroid hormones
• Population prevalence of overt hypothyroidism is 0.3%, while subclinical hypothyroidism may be found in 4%
• Men: women = 1:10

Causes of hypothyroidism (pg 757, table 20-3)

PRIMARY
• Developmental (thyroid dysgenesis: PAX8, FOXE1, TSH receptor mutations)
• Thyroid hormone resistance syndrome (THRB mutations)
• Post ablative (surgery, radioiodine therapy or external radiation)
• Autoimmune hypothyroidism - Hashimoto thyroiditis
• Iodine deficiency
• Drugs (lithium, iodides, p-aminosalicylic acid)
• Congenital biosynthetic defect (dyshormonogenetic goiter)
SECONDARY
• Pituitary failure
TERTIARY
• Hypothalamic failure (rare)

Hypothyroidism
Etiology/Pathogenesis

• Primary hypothyroidism is the most common cause of hypothyroidism and can be accompanied by enlargement of the gland (goiter)
• As detailed in the previous slide primary hypothyroidism may be congenital, acquired or autoimmune
• Worldwide congenital hypothyroidism is most often due to endemic iodine deficiency in the diet
• In iodine-sufficient areas, the most common cause of hypothyroidism is chronic autoimmune thyroiditis (Hashimoto’s thyroiditis)
• Classic clinical manifestations include cretinism and myxedema
Hypothyroidism

**Cretinism**
- Hypothyroidism in infants or early childhood
- Secondary to iodine deficiency (endemic) or rarely from inborn errors in metabolism
- Impaired development of skeletal system and CNS with severe mental retardation, short stature, coarse facial features, a protruding tongue and umbilical hernia

**Hypothyroidism**

**Myxedema**
- Adult hypothyroidism
- Gradual slowing of mental and physical activity
- Fatigue, lethargy, apathy, slowed speech
- Cold intolerance and reduced sweating
- Overweight and constipation
- Periorbital edema, thick coarse skin, enlarged tongue (deposition of glycosaminoglycans)
- Reduced cardiac output causes shortness of breath and decreased exercise capacity
- Promotes an atherogenic profile, (increased total cholesterol and LDL) leading to adverse cardiovascular mortality rates

**Hypothyroidism**

**Laboratory Findings**
- Decreased T4
- TSH levels – most sensitive screening test for hypothyroidism
- Primary hypothyroidism
  - Increased TSH
- Secondary hypothyroidism
  - Decreased / normal TSH
Thyroiditis

- Inflammation with pain, sometimes severe
  - Infectious thyroiditis
  - Subacute granulomatous thyroiditis (De Quervain thyroiditis)
  - Relatively little pain
    - Subacute lymphocytic thyroiditis
    - Reidel’s thyroiditis
    - Hashimoto’s thyroiditis

Hashimoto Thyroiditis

- Most common cause of hypothyroidism in non-iodine deficient areas
- Characterized by gradual thyroid failure because of autoimmune destruction of the thyroid gland: hypothyroidism
- Prevalent between 45-65 years of age, more common in women (men: women = 1: 10 to 20)
- Major cause of non endemic goiter in pediatric age group
- Strong genetic component supported by concordance in 40% of monozygotic twins and presence of circulating antibodies in 50% of asymptomatic siblings of patients with Hashimoto’s disease
Hashimoto Thyroiditis

- Laboratory findings will show Antibodies to:
  - Thyroglobulin and Thyroid Peroxidase (TPO)
  - TSH Receptor
  - Iodine Receptor

Hashimoto thyroiditis

- Diffusely enlarged gland
- Intact capsule
- Well demarcated from adjacent structures
- Cut surface is pale, yellow tan, somewhat nodular and firm

Hashimoto thyroiditis

- Thyroid parenchyma infiltrated by mononuclear inflammatory cells
  - The small blue cells are the lymphocytes
  - The more pink cells forming a follicle with colloid in the middle are residual follicular cells
3/18/2019

- Thyroid follicles lined by Hürthle cells / oncocyes which have abundant granular pink cytoplasm (due to cells containing numerous mitochondria)
- Formation of germinal centers

Hashimoto thyroiditis

Hashimoto Thyroiditis – clinical course

- Painless enlargement of the gland with some degree of hypothyroidism
- In the usual clinical course hypothyroidism develops gradually
- Some patients may develop a transient hyperthyroidism due to disruption of thyroid follicles with release of thyroid hormones (hashitoxicosis) – elevated T4 and T3, reduced TSH and reduced 131 uptake
- Gradually hypothyroidism supervenes
- Increased risk of developing other autoimmune diseases
- Increased risk of developing Non Hodgkin B cell lymphoma
- Relationship between Hashimoto and development of thyroid epithelial cancers (papillary cancer) is controversial

Subacute/ Granulomatous (DeQuervain) Thyroiditis

- 40-50 years of age
- Female predominance (men: women= 1:4)
- Viral or post-viral inflammatory response
- Viral antigens or virus-induced host tissue damage stimulates formation of cytotoxic T cells which then damage the thyroid follicular cells (process is self-limited)
### Granulomatous / De Quervain Thyroiditis

- Most common cause of thyroid pain
- Variable enlargement of thyroid
- History of upper respiratory infection
- Transient hyperthyroidism usually diminishing in 2 to 6 weeks
- During the hyperthyroid phase elevation of T4, T3, decreased TSH, however radioactive iodine uptake is diminished
- Recovery and normal thyroid function in 6 to 8 weeks

### Subacute Lymphocytic (Painless) Thyroiditis

- Usually in middle aged women
- Comes to clinical attention due to mild hyperthyroidism, goitrous enlargement of the thyroid or both
- Process resembling painless thyroiditis can occur during the postpartum period in up to 5% of women
- Painless and postpartum thyroiditis are variants of Hashimoto thyroiditis since majority of patients have circulating antibodies and/or a family history of autoimmune diseases
- Vast majority of patients are euthyroid by one year
- 1/3 of patients progress to overt hypothyroidism over 10 years
- Pathology – mild enlargement of thyroid, lymphocytic infiltration with germinal centers however no fibrosis or Hürthle cell metaplasia
Riedel thyroiditis

- Rare disorder of unknown etiology
- Extensive fibrosis involving the thyroid and contiguous neck structures
- Hard and fixed mass – clinically simulating cancer
- Maybe associated with idiopathic fibrosis at other sites like retroperitoneum
- Presence of circulating antibodies – autoimmune etiology
- (Considered to be an IgG4 related disease)

Graves Disease

- Most common cause of endogenous hyperthyroidism
- Triad of findings
  1. Hyperthyroidism due to diffuse hyperfunctional enlargement of thyroid
  2. Infiltrative ophthalmopathy – exophthalmos
  3. Infiltrative dermopathy – pretibial myxedema (present in a minority of patients)
- M:F = 1:10
- Between ages 20-40 years old
- Common – 1.5-2% of US women

Graves Disease

Etiology/Pathogenesis

- Autoimmune disease – over 30 to 40% concordance in monozygotic twins as compared to 5% in dizygotic twins
- Multiple autoantibodies
  - Thyroid stimulating immunoglobulin (TSI)- binds to TSH receptor and mimics its action (relatively specific for graves disease)
  - Thyroid growth-stimulating immunoglobulin (TGI) – cause proliferation of the follicular epithelium
  - TSH-binding inhibitor immunoglobulin (TBII)
Graves disease

- Symmetrically enlarged gland
- Weight may be >80 grams
- Soft meaty appearance of the parenchyma on cut surface

Graves disease

- Crowded and tall follicular cells
- Formation of small papillae filling the lumen of the follicles
- Papillae do not contain fibrovascular cores
- Pale colloid with scalloped margins
- Lymphoid infiltrate with germinal centers common

Graves Disease
Clinical Manifestations

- Thyrotoxicosis
- Thyroid gland enlargement
- Wide staring gaze and lid lag – sympathetic overactivity
- Infiltrative ophthalmopathy - Exophthalmos
- Infiltrative dermopathy - Pretibial myxedema
- Risk of other autoimmune diseases
• Protuberant appearance of the eye because of accumulation of loose connective tissue behind the eyeball
• Weak extraocular muscles

Infiltrative ophthalmopathy

• Skin overlying the shins
• Scaly thickening and induration
• Present in a minority of patients

Infiltrative dermopathy - Pretibial myxedema

Graves Disease
Laboratory Findings

• Increased serum levels of total thyroid hormones, free T3 and free T4
• Decreased TSH
• Increased radioactive iodine uptake with diffuse uptake on radioiodine scans
Graves Disease

Treatment

- Beta blockers – symptomatic treatment of increased adrenergic tone (tachycardia, palpitations, tremulousness, anxiety)
- Propylthiouracil (thiourea): decreases thyroid hormone synthesis
- Radioiodine ablation
- Surgery
• Goiter – enlargement of the thyroid
• (Non toxic – not associated with hyperthyroidism)
• Impaired synthesis of thyroid hormone
• Decrease T4 and T3 and increased TSH causing hyperplasia and hypertrophy of follicular epithelium
• Diffuse (simple) Multinodular
• Endemic (>10% of population affected – mountainous regions)
• Sporadic - female predominance at puberty

Diffuse / Nontoxic (simple) Goiter
• Enlargement of the entire gland without producing nodularity
• Diffuse symmetric enlargement
• Usually 100 to 150 grams
• Cut surface - brown, glassy and translucent
• Microscopically two phases
  • Hyperplastic phase – enlarged thyroid gland with crowded follicular cells (not shown)
  • Colloid involution – some follicles are distended
  • Some are small
  • Entire gland shows flattened epithelium and follicles filled with colloid

Diffuse Nontoxic (simple) Goiter

Diffuse Nontoxic Goiter – clinical course
• Vast majority of patients euthyroid
• Mass effect – large thyroid may press on trachea, esophagus and also cause cosmetic disfigurement
• Normal T4 and T3
• Elevated TSH or in the upper limit of normal

Multinodular Goiter
• Asymmetric enlargement with numerous nodules
• Evolvement from diffuse goiters over many years due to repeated episodes of hyperplasia and involution
• Older adults
• Similar epidemiology to diffuse goiters
• Commonly mistaken for neoplasm
• Some cells within a nodule may become autonomous and continue proliferating
• Both polyclonal and monoclonal nodules occur within the same gland
• May be toxic or non toxic
Multinodular goiter

- Asymmetric multinodulated gland
- Maybe - 2000 gm in weight
- One lobe may be more involved than the other
- Intrathoracic or plunging goiter – grows behind the sternum and clavicles

Multinodular goiter

- Cut section – irregular nodules containing gelatinous colloid
- Foci of fibrosis and calcification (gritty sensation when cutting)
Multinodular goiter

- Colloid rich follicles lined by flattened inactive epithelium
- Areas of follicular hyperplasia (do not have a prominent capsule between the hyperplastic nodule and adjacent parenchyma which is a feature of follicular neoplasms)

Multinodular Goiter – clinical features

- Mass effect with disfigurement or compression of adjacent organs
- Most patients euthyroid
- Minority may develop toxic multinodular goiter due to development of an autonomous nodule (Plummer’s syndrome)
- Risk of malignancy is <5%
- Uneven radioactive iodine uptake
- Is the mass benign or malignant? – Fine needle aspiration
Neoplasms

- Major concern for patients presenting with thyroid nodules
- 15,000 new cases of thyroid cancer per year in the U.S.
- Mostly indolent, with 90% survival at 20 years
- Single, solitary nodules are more likely to be neoplastic
- Nodule in young patients are more likely to be neoplastic
- Nodules in males are more likely to be neoplastic
- Nonfunctioning "cold" nodule more likely to be neoplastic
- History of radiation to the head and neck area is associated with increased incidence of thyroid malignancy

Follicular adenoma (FA)

- Discrete solitary masses derived from follicular epithelium
- Somatic mutations of RAS or PAX8-PPARG fusion gene in 20% (similar mutations seen in follicular carcinomas, hence some FA may undergo malignant transformation)
- Somatic mutations of TSH receptor signaling pathway may be found in >50% of toxic adenomas (rare in follicular carcinomas hence toxic adenoma donot seem to undergo malignant transformation)

Follicular adenoma

- Solitary, encapsulated, spherical mass
- Well-demarcated from adjacent thyroid
- Usually average about 3 cm but may be larger
- Gray-white to red brown mass
Follicular adenoma

- Bulges above the cut surface
- May have areas of hemorrhage, necrosis or calcification

Follicular adenoma (FA)

- Neoplastic cells arranged in closely packed follicles
- Demarcated from the adjacent thyroid parenchyma
- By a well defined capsule
- The presence of well defined intact capsule is important in distinguishing FA from hyperplastic nodules of multinodular goiter

Follicular adenoma (FA)

- Uniform small follicles (micro follicles) which contain colloid, like seen in the adjacent picture
- Extensive mitotic activity, necrosis or high cellularity warrants search for a follicular carcinoma as well as evaluation of nuclear features to exclude a follicular variant of papillary carcinoma
Hürthle cell / oxyphil / oncocytic adenoma

- Follicular adenoma with cells bearing abundant pink granular cytoplasm due to presence of abundant mitochondria
- Clinical presentation and behavior no different than a conventional FA

Follicular Adenoma

- The buzz word is “capsule” which should be well defined and intact
- The criteria for differentiating a follicular adenoma from carcinoma is demonstration of capsular or vascular invasion
- Requires histologic examination of the entire nodule for diagnosis and cannot be rendered on a needle core biopsy or Fine needle aspiration
- Hence on small samples - render a diagnosis of follicular neoplasm (can be adenoma or carcinoma)

Follicular Adenoma – clinical features

- Painless asymptomatic mass – on routine exam
- May produce local symptoms – large masses
- Usually “cold” on radioactive iodine scan
- Rarely functioning toxic adenoma
- Treatment is lobectomy
- Excellent prognosis – do not recur or metastasize
Carcinomas

- Uncommon malignancy in the US, 1.5% of all cancers
- >F in early and middle adult age group
- M=F, cancers in childhood and late adult life
- Major subtypes and their relative frequencies are
  1. Papillary Carcinoma, 75-85%
  2. Follicular Carcinoma, 10-20%
  3. Medullary Carcinoma, 5% (parafollicular C cells)
  4. Anaplastic Carcinoma, less than 5%
- Linked with ionizing radiation and dietary iodine deficiency
- Molecular genetic events

Papillary Carcinoma

- Most common thyroid cancer
- Occurs throughout life, commonly 25 – 50 years of age
- Account for majority of thyroid cancers associated with history of radiation exposure
- Marked increase in the incidence during the last 30 years due to recognition of follicular variant

Papillary Carcinoma

- Solitary or multifocal lesion
- (The adjacent picture shows two foci - two small red arrows)
- May be well-circumscribed and encapsulated or may be ill-defined and infiltrative
- Cut surface shows papillary structures
- Foci of fibrosis and calcification seen
- Cystic papillary carcinomas show a cyst with an intratumoral nodule

Papillary carcinoma
Papillary carcinoma

• Branching papillae with fibrovascular cores lined by multiple layers of cuboidal to columnar epithelium

Papillary carcinoma

• Papillae with fibrovascular cores (transverse section)

Papillary carcinoma

• Diagnosis based on nuclear features
• Longitudinal nuclear grooves (looks like lines along the long axis of the nucleus)
• Ground glass or Orphan Annie eyed nuclei (due to finely dispersed chromatin)
Intranuclear cytoplasmic inclusions (red arrows) which are invaginations of the cytoplasm into the nucleus.

Nucleolus is marginalized to the periphery and is close to the nuclear membrane.

Psammoma bodies (red arrows) which are calcified lamellated concretions usually seen in the cores of the papillae.

Over a dozen histologic variants.
- The one most liable for misdiagnosis is “follicular variant” FVPTC which has follicular architecture (no papillae seen).
- The diagnosis of FVPTC is based on nuclear features.
- FVPTC - frequently encapsulated, lower incidence of lymph node and extrathyroidal metastasis and favorable prognosis (term replaced by Noninvasive follicular lesion with papillary-like nuclear features, NIFT-P).
- Tall cell variant – tall columnar cells with intense eosinophilic cytoplasm lining the papillary structures, aggressive behavior.
- Diffuse sclerosing variant – younger individuals including kids.
- Papillary microcarcinomas (less than 1 cm, may be incidental finding in surgery).
Papillary Carcinoma

- May present as asymptomatic thyroid nodules or as lymph node metastasis
- Cold on scintiscans
- Diagnosed by fine needle aspiration cytology
- Total thyroidectomy with excision of abnormal appearing lymph nodes
- Good prognosis, >95% ten-year survival
- Isolated cervical lymph node metastasis does not have an effect on prognosis
- Prognosis depends on several factors including age (>40 years less favorable), extrathyroid extension and distant metastasis (stage)

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Papillary carcinoma – genetic events

- Rearrangements of RET - chromosome 10q11 with RET/PTC translocations are present in 20 to 40% of papillary cancers
- Paracentric inversions or translocations of NTRK1 (chromosome 1q21) are seen in 5 to 10%
- 1/3 to 1/2 of papillary cancers have mutations in BRAF gene, which correlates with adverse prognostic factors

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Follicular Carcinoma

- Second most common thyroid cancer – account for 5 to 15% of all thyroid cancers
- Presents at an older age, 40 to 60
- Male: Female = 1:3
- Higher incidence in iodine deficient area
- May be minimally invasive or widely invasive
**Follicular carcinoma**

- Single well-circumscribed nodule largely replacing almost the entire lobe.
- Nodule has a light tan appearance and contains small foci of hemorrhage.
- These sharply demarcated lesions may be difficult to distinguish from follicular adenomas grossly.
- Larger/widely invasive tumors may extend well beyond the capsule to involve the adjacent neck structures.

**Microscopy**

- Microscopically composed of fairly uniform follicular cells forming follicles containing colloid.
- Some cancers may have nests and sheets of cells with less apparent follicular differentiation.
- Tumors with granular pink cytoplasm areHurthle cell or oncocytic variant of follicular carcinomas.
- Absence of typical nuclear features of papillary carcinoma, no psammoma bodies seen.

**Minimally invasive**

- Focal capsular or vascular invasion.
- Requires extensive sampling of the tumor capsule interface.
- For capsular invasion – mushrooming of the tumor through the full thickness of the capsule.
Follicular carcinoma

- Tumor
- Capsule
- Capsular vessel with tumor
- The black arrow marks the endothelial lining of the vessel
- Vascular invasion – applicable to vessels in the capsule or beyond
- Presence of tumor plugs within the intratumoral vessels has no prognostic significance

Follicular Carcinoma – clinical course

- Slowly enlarging painless nodule – cold on scintiscans
- Hematogenous metastasis to bone, lungs, liver etc
- Treatment – total thyroidectomy with radioactive iodine
- Prognosis depends on extent of invasion
- Widely invasive follicular carcinomas presenting with metastasis may succumb to their disease within 10 years
- Minimally invasive follicular carcinomas have >90% 10 year survival

Follicular carcinoma – genetic events

- 1/3 to 1/2 of follicular carcinomas harbor mutations in the PI3K/AKT pathway
- Another 1/3 to 1/2 have translocation (2;3) (q13;p25) resulting in PAX8/PPARG fusion product
Medullary Carcinoma

- Neuroendocrine neoplasms derived from the parafollicular or C cells
- Account for 5% of thyroid neoplasms
- May secrete calcitonin or other polypeptide hormones like ACTH or VIP
- 70% sporadic, 30% familial or associated with MEN syndrome 2A or 2B
- Cases associated with MEN occur in the first decade while sporadic and familial medullary carcinomas arise in the 4th or 5th decade
- Tumor may be single (more likely sporadic) or multiple (familial or MEN associated)

Medullary carcinoma

- Solid grey tan tumor with no well defined capsule with infiltration of adjacent thyroid parenchyma
- Larger lesions with foci of hemorrhage and necrosis

Medullary carcinoma

- Polygonal to spindle shaped cells forming nests, trabeculae and follicles
- Acellular amyloid deposit derived from calcitonin
- Amyloid can be demonstrated by Congo red or immunohistochemical stains
- Familial medullary cancers have prominent clusters of C-cells throughout the parenchyma
Medullary Carcinoma

- Demonstration of amyloid with Congo Red staining which imparts a reddish color to the amyloid
- Congo red stained amyloid gives an apple green birefringence under polarized light

Medullary Carcinoma

- May present as a mass or patients may be asymptomatic
- Some instances - present with paraneoplastic syndrome like diarrhea (VIP), Cushing syndrome (ACTH)
- Patients with MEN (RET gene) syndrome may come to clinical attention due to endocrine neoplasms in other organs
- Hypocalcemia – not a prominent feature despite secretion of calcitonin
- Medullary carcinomas arising in MEN 2B are more aggressive
- Treatment includes total thyroidectomy
- Calcitonin and CEA used as tumor markers
- Asymptomatic MEN -2 kindred with RET mutations are offered prophylactic thyroidectomy as early as possible

Anaplastic Carcinoma

- Undifferentiated tumors accounting for 5% of thyroid tumors
- Mean age of 65 years
- Mortality approaches 100%, with most patients dying in less than one year
Anaplastic carcinoma

- Neoplasm composed of highly anaplastic cells
- Spindle cells
- Giant cells
- Mixed spindle and giant cells
- Foci of papillary or follicular differentiation may be seen in 1/3 suggesting their origin from better differentiated tumor
- Mitotic figure

Anaplastic carcinoma

- Tumor composed of spindle cells
- Brown stain depicts positive immunohistochemical staining for cytokeratin
- Tumors may not stain for thyroglobulin

Anaplastic carcinoma

- Presents as a rapidly enlarging bulky mass
- Usually the disease has spread beyond thyroid into adjacent structures of the neck at presentation
- Symptoms include dysnea, dysphagia, hoarseness and cough due to compression of neck structures
- No effective therapy
- Usually death occurs in <1 year due to local aggressive growth and compromise of vital structures
- Genetic events – inactivation of p53 or activating mutations of beta catenin
Thyroglossal duct / cyst

- Most common clinically significant congenital anomaly
- Incomplete atrophy of the duct
- Presents at any age as a midline cyst or an anterior mass
- Lined by benign epithelium with normal thyroid and lymphocytes in the wall
- Infection with risk of abscess formation

A 49-year-old woman has had increasing cold intolerance, weight gain of 4 kg, and sluggishness over the past two years. A physical examination reveals dry, coarse skin and alopecia of the scalp. Her thyroid is not palpably enlarged. Her serum TSH is 11.7 UU/mL (ref range 0.4 -4.4 UU/ml) with thyroxine of 2.1 ug/dL (ref range 5-11 ug/dL). A year ago, anti-thyroglobulin and anti-microsomal autoantibodies were detected at high titer. Which of the following thyroid diseases is she most likely to have?

A) DeQuervain disease  
B) Papillary carcinoma  
C) Hashimoto thyroiditis  
D) Nodular goiter  
E) Graves disease

A 40-year-old woman notes increasing enlargement and discomfort in her neck over the past week. She sees her physician, who palpates diffuse, symmetrical enlargement with tenderness in the region of the thyroid gland. Thyroid function tests show serum TSH of 0.8 mU/mL (ref range 0.4 -4.4 UU/ml) and thyroxine of 14.9 ug/dL (ref range 5-11 ug/dL). The physician refers the patient to an endocrinologist, but the next available appointment is in 8 weeks. When the endocrinologist examines the patient, the thyroid is no longer palpable and there is no pain. Repeat thyroid function tests reveal a serum TSH of 3.8 UU/mL and thyroxine of 5.7 ug/dL. Which of the following thyroid diseases is most likely to produce these findings?

A) Nodular goiter  
B) Non-Hodgkin lymphoma  
C) DeQuervain disease  
D) Hashimoto thyroiditis  
E) Graves disease  
F) Riedel thyroiditis
A 35-year-old woman has had insomnia for the past 4 months. She has also had episodes of diarrhea with up to 4 loose stools per day. On physical examination, she exhibits bilateral lid lag and wide staring gaze. Her outstretched hands demonstrate a fine tremor. On palpation of her neck, the thyroid gland does not appear to be enlarged and no masses are palpable. Laboratory studies show a serum TSH of 10.8 UU/mL (ref range 0.4-4.4 UU/ml) in association with a serum free thyroxine of 5.1 ng/dL (ref range 0.8-1.7 ng/dl). Which of the following is the most likely diagnosis?

A) Graves disease  
B) Pituitary adenoma  
C) Chronic thyroiditis  
D) Prior thyroidectomy  
E) Nodular goiter

A 30-year-old woman from Barcelona has noted enlargement of her neck over the past 4 months. On physical examination, she has a diffusely enlarged thyroid that is not painful to palpation. Her TSH level is 0.2 mU/L. A subtotal thyroidectomy is performed and histologically the tissue shows follicles with papillary infoldings lined by tall columnar cells. Which of the following is the most likely diagnosis?

A) Subacute granulomatous thyroiditis  
B) Papillary carcinoma  
C) Multinodular goiter  
D) Hashimoto thyroiditis  
E) Graves disease

Questions

http://library.med.utah.edu/WebPath/EXAM/MULTORG/end1frm.html

(source of questions)

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