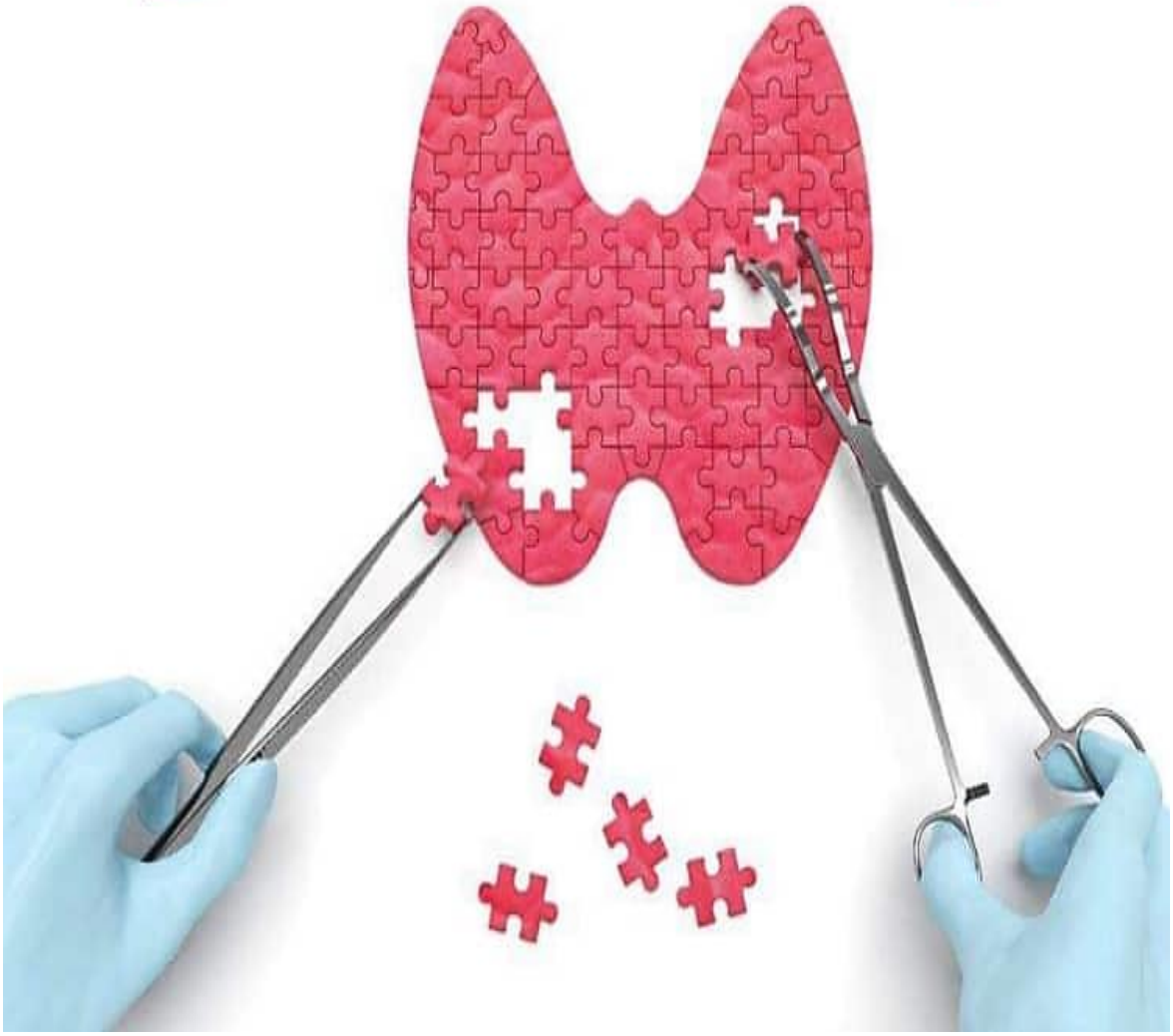
لجان الدفعات
كلية الطب
الجامعة الأردنية

ENDOCRINE SURGERY



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***Note: Information from the old dossier were used, thanks Dr. Fared Halteh.**

Head and Neck

Anatomy:

❖ **Layers of the neck (superficial to deep):**

- Skin
- Subcutaneous tissue
- Superficial fascia which encloses the platysma muscle. It also contains superficial lymph nodes.
- Deep cervical fascia and muscles

❖ **The neck is divided into:**

- **Anterior compartment (organic compartment):** made of two triangles; anterior and posterior, separated by the sternocleidomastoid muscle.
- **Posterior compartment (muscular compartment):** important in neurosurgery (will not be discussed here)

❖ **Subdivisions of the organic (anterior) compartment:**

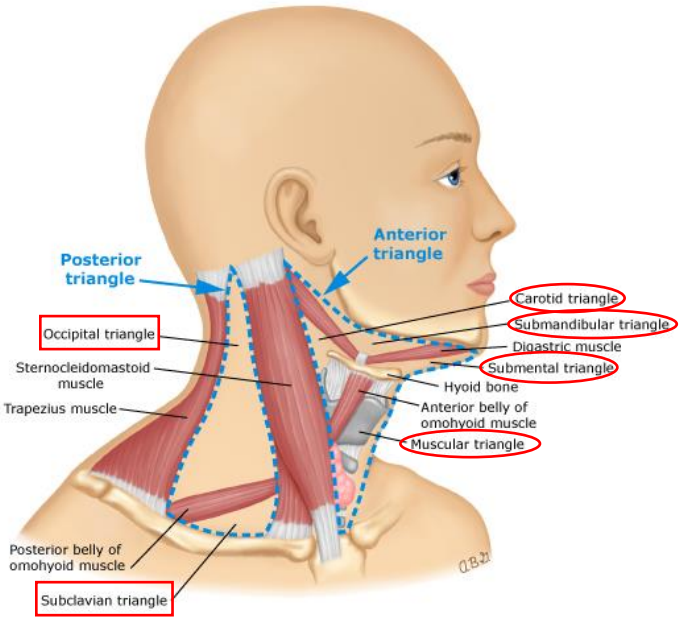
1) **Anterior triangle:**

Borders:

- Superior: inferior border of the mandible
- Medial: midline of the neck
- Lateral: anterior border of sternocleidomastoid

Important structures:

- Hyoid bone:
  - forms the attachment of many important muscles which lie on the floor of the mouth.
  - Divides the muscle into suprahyoid and infrahyoid (strap) muscles.
- Thyroid gland
- Parathyroid glands
- Larynx
- Trachea
- Common carotid artery and its branches
- Internal jugular vein
- Vagus nerve and recurrent laryngeal nerves



Subdivisions:

Subdivision	Boundaries	Important structures
Submental triangle (unpaired)	• Mandibular symphysis • Anterior belly of digastric muscle • Body of hyoid bone	▪ Submental lymph nodes
Submandibular triangle (paired)	• Lower border of mandible • Anterior belly of digastric muscle • Posterior belly of digastric muscle	▪ Submandibular gland and duct ▪ Submandibular lymph nodes ▪ Facial artery and vein
Carotid triangle (paired)	• Posterior belly of digastric muscle • Superior belly of omohyoid muscle • anterior border of sternocleidomastoid	▪ Common carotid artery ▪ External and internal carotid arteries ▪ Internal jugular vein ▪ Vagus (X), accessory (XI) and hypoglossal (XII) nerves
Muscular triangle (paired)	• Midline of neck • Superior belly of omohyoid muscle • anterior border of sternocleidomastoid	▪ Strap muscles: Omohyoid, sternohyoid, sternothyroid and thyrohyoid muscles *Note: Sternohyoid lies superficial to sternothyroid* ▪ **Thyroid and parathyroid glands**

2) **Posterior triangle:**

Borders:

- **Anterior**: posterior border of sternocleidomastoid
- **Posterior**: anterior border of trapezius
- **Inferior**: middle portion of the clavicle
- **Apex**: occipital bone

Contents:

- **Levator scapula:** a muscle that elevates the scapula
- **Scalene muscles:** attach to the ribs and originate from the lateral process of the cervical vertebra
- **Subclavian vein and artery**
- **External jugular veins**
- **Branches of the cervical plexus**
- **Accessory nerve** (innervates the **trapezius**)

Subdivisions:

- Occipital triangle
- Supraclavicular triangle

❖ **Platysma muscle:**

- One of the muscles of facial expression
- Attached to the clavicle and ribs inferiorly and to the mandible and mastoid process superiorly
- It disappears in the midline
- It is innervated by the cervical branch of the facial nerve
- Upon reaching the parotid gland, it will slip to engulf the parotid forming the parotid fascia. This fascia is strong and cannot be stretched; thus, any swelling in the parotid gland will cause severe pain.
- It continues downward to engulf the sternocleidomastoid muscle
- It is not well developed in females; however, in males it is well developed due to the process of shaving.

Landmarks in the midline:

- Hyoid bone
- Thyroid cartilage
- Cricoid cartilage (the only complete ring of cartilage around the trachea)

❖ **Deep fascia of the neck (deep cervical fascia):**

A. Pretracheal fascia; holds the following structures together:

- Thyroid gland
- Larynx
- Trachea
- Esophagus
- Infrahyoid muscles

B. Prevertebral fascia:

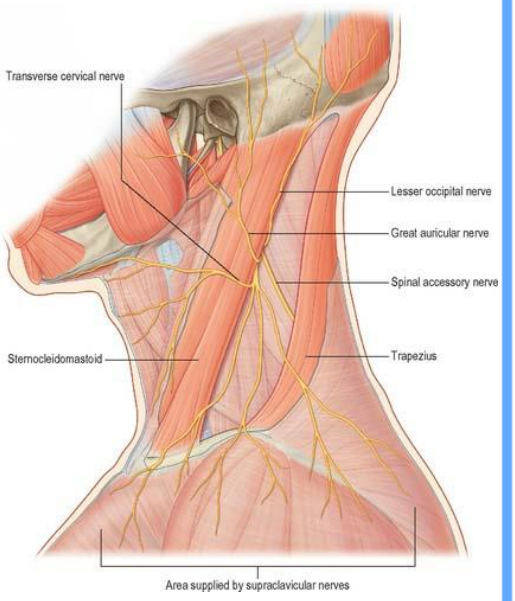
- It surrounds the vertebral column and the muscles associated with it.
- Branches of the cervical plexus run deep to this layer of fascia

C. Carotid sheath; contents (on each side):

- Common carotid and internal carotid arteries
- Internal jugular vein
- Vagus nerve (lies posterior to the artery and the vein)

❖ **Sensory innervation of the neck:**

- Mediated by the cutaneous branches of the cervical plexus.
- These branches emerge behind the sternocleidomastoid muscle forming a cross
  - **Greater auricular nerve: upwards**
    - Innervates the skin of parotid area and ear pinna
    - Runs along with external jugular vein
  - **Anterior cervical nerve:**
    - Also known as the transverse cervical nerve
    - Runs anteriorly
  - **Lesser occipital nerve:**
    - Runs posteriorly
    - Innervates the posterior aspect of the neck



- **Supraclavicular nerve:**
  - Downwards
  - Divides into medial, intermediate and lateral branches.
  - Innervates the shoulder area
  - Shares exit with the **phrenic nerve (C5 root**). That is why patients with **gallbladder** problems have pain referred to the shoulder area.

The neck is rich in blood vessels, so wounds in this area heal **quickly**.

❖ **<u>Lymphatic drainage of the neck</u>**

- It is important to know the primary lymphatic drainage of each area of the neck because most cancers in this area are first transmitted via **lymphatics**.
- 1/3 of the body's lymph nodes are found in the head and neck.
- If lymph nodes are red and tender think of **inflammation**; however, if they are painless, think of **malignancy**.
- Lymph nodes are found in the fatty tissue or plates around the **jugular vein**.
- Lymphatics of the neck are divided into:

A. Superficial group: they are felt under the skin.

- Buccal (facial) nodes
- Preauricular (parotid) nodes: embedded inside the parotid gland
- Mastoid (retroauricular) nodes
- Occipital nodes
- Superficial cervical nodes: These lie along the course of the external jugular vein on the superficial surface of the sternocleidomastoid muscle

B. Deep cervical group: run along the course of the internal jugular vein within the carotid sheath. They are divided into 6 levels; I, II, III, IV, V & VI.

- **Group I:**
  - **Ia: submental nodes**; drain midline structures:
    - Tip of the nose / Middle portion of upper and lower lips
  - **Ib: submandibular nodes**
    - Nose / Sides of the tongue

- **Group II: upper jugular (Jugulo-digastric)**
  - Lie behind the posterior belly of digastric muscle

- **Group III: middle jugular (jugular omohyoid)**
  - Lie behind the omohyoid

- **Group IV: lower jugular (epithelio-cervical)**
  - Lie below the omohyoid

- **Group V: accessory**
  - Found in the posterior triangle of the neck, related to the accessory nerve.
  - Accessory lymph nodes drain the post-nasal space.

- **Group VI: tracheo-esophageal (paratracheal)**
  - Lie between the trachea and cervical esophagus
  - Drain thyroid and subglottic larynx
  - **Subglottic laryngeal carcinoma** will metastasize to this group

Notes:

- Drainage of the tongue:
  - Posterior 1/3: **occipital** lymph nodes
  - Sides of the tongue: **submandibular** lymph nodes (**Ib**)
  - Bulk of the tongue: jugulo-digastric (**II**)
- Drainage usually starts from the most superficial lymph nodes and moves to the deeper ones in a consequential fashion. Because of this pattern of drainage, it is possible to stop a malignancy from spreading by interrupting this route. This can be done through surgery, radiotherapy, or lymphatic compression.

❖ Neck dissection:

1. **Radical dissection:**
   - Removal of:
     - Lymph nodes levels I-V
     - Fat plates
     - Sternocleidomastoid, digastric, stylohyoid & omohyoid muscles.
     - Submandibular gland and tail of parotid
     - Internal jugular vein
     - Accessory nerve & cervical plexus sensory nerves
   - Indications:
     - **Extensive** cervical involvement or matted lymph nodes with extracapsular spread
     - Invasion into sternocleidomastoid, internal jugular vein, or accessory nerve

2. **Modified radical dissection:**
   - Excision of lymph nodes in levels I-V with sparing all or some of the non-lymphatic structures (**spinal accessory nerve**, **internal jugular vein** and/or **sternocleidomastoid muscle**), **Contraindicated** in presence **distant metastases** or **fixation** of vital structures (e.g. carotid artery).

3. **Selective dissection:**
   - here one or more of the LNs I-V are preserved based on the location of the tumor.

   a. Supraomohyoid:
   - Removal of groups I-III
   - In cases of squamous cell carcinoma (effective in 30-80% of cases)

   b. Anterior dissection (extended supraomohyoid):
   - Removal of groups I-IV

   c. Lateral dissection:
   - Removal of groups II-IV

d. Posterolateral dissection:

- Removal of groups II-V

e. Posterior dissection:

- Removal of group V only, Done in cases of **pharyngeal** carcinoma

f. Central (median) dissection:

- Removal of group VI

❖ **Complications of neck dissection:**

- Removal of both jugulars → edema
- Removal of accessory nerve → **shoulder drop** due to a loose trapezius
- Removal of sternocleidomastoid → **disfigurement**: treated by physiotherapy to activate surrounding muscles
  Removal of sternocleidomastoid will ***not* affect movement of the head.

❖ **Sentinel lymph nodes:**

- The first lymph node to drain the tumor.
- To detect it, the tumor is injected with methylene blue. The dye is then followed until it reaches the first lymph node.
- The lymph node is excised and tested via a probe that detects nuclear activity. A positive blue node confirms that the excised node is **the sentinel node.**
- If positive, **neck dissection is performed**

❖ Notes:

- Supraclavicular lymph nodes are found in the supraclavicular fossa. They are involved in malignancies of lung and breast; not those of head and neck.
- **Virchow's lymph nodes** (left supraclavicular lymph nodes) drain stomach and abdominal carcinomas (can indicate pancreatic or gastric CA).
- Papillary thyroid carcinoma will drain to groups III and IV
- Tonsils drain to group II

❖ Staging LN masses:

- T1: <3 cm
- T2: 3-6 cm
- T3: >6 cm
- **T4: bilateral**

❖ Diagnosis:

- CT: 90% accuracy
- Examination under anesthesia
- MRI: not routine, but better than CT
- Biopsy
- FNA: usually performed on any enlarged lymph node

Branchial anomalies

INTRODUCTION

- Branchial anomalies are anomalies that represent, in the majority of cases, **remnants of the second branchial cleft.** They are usually present at birth, although they may not become apparent for several years.
- During embryogenesis, the branchial arches are found in the area of the neck in the pharynx.
- Normally, these arches disappear before birth except for:
  - **1st branchial cleft:** external auditory meatus
  - **1st pouch:** Eustachian tube and tympanic cavity
  - **The area in between the 1st branchial cleft and 1st pouch:** tympanic membrane
  - **1st arch**: bones of the middle ear (amongst others)
- Branchial apparatus develops from **ectoderm** and **endoderm**. The branchial clefts arise from ectoderm, while branchial pouches arise from endoderm.
- Remnants of the branchial apparatus present after birth are called **vestigial parts**

ETIOLOGY

Down's syndrome is a hereditary disorder, but it is accompanied with some congenital anomalies in the GIT and CVS

- They are divided into:
  - **Hereditary/familial**: occur due to genetic abnormalities
  - **Congenital:**
    - Occur due to failure of organogenesis
    - Usually occur during **the 1st trimester**
    - Influenced by drugs, radiation, infections, and genetic abnormalities

Types:

1. **Branchial cyst:**
   - Branchial cysts are painless, firm, mobile swellings that occur on the lateral aspect of the upper neck along the sternocleidomastoid muscle, has a smooth and globular surface (can be aspirated). It has a deep tract that travels between the internal and external carotid artery to the tonsillar fossa.
   - They account for almost 20% of pediatric neck masses and **1/3 of congenital masses**.
   - Branchial cleft cysts are subdivided based on the developmental origin into:
     - **Dermoid** (ectoderm):
       - More common
       - Lined by skin
       - Contains cholesterol (yellow pus-like fluid)
     - **Mucous** (endoderm):
       - Lined by a mucous membrane
       - Contains mucous secretions

- Differential diagnosis:
  - Parotid swelling (superficial to sternocleidomastoid)
  - Enlarged lymph nodes (deep to sternocleidomastoid)
  - Cold tuberculous abscess (rare)

- Site of presentation:
  - Most commonly arises from the ***2nd branchial cleft*:**
    - The cysts are relatively consistent in their location in the neck.
    - In the anterior triangle deep to sternocleidomastoid, so it disappears on muscle contraction.
    - At the level of the junction between the upper and middle third of the sternocleidomastoid muscle
  - If it arises from the *1st branchial cleft*, it presents near the angle on mandible or around the ear. It might be associated with facial nerve or ear canal involvement
  - If it arises from the *3rd branchial cleft* it presents on the lower aspect of the neck with tracts that end on the thyrohyoid membrane or in the pyriform sinus.

- Age of presentation:
  - They usually present in **late childhood or early adulthood** when a previously unrecognized cyst becomes infected. Only a very small percentage first present in adulthood.

- Clinical presentation:
  - They usually lie dormant and unnoticed until they become infected, often with a history of **preceding upper respiratory infection**. This will lead to enlargement of the lymphatics accompanied by hypersecretion which will cause the cysts to enlarge.
  - If the inflammation was strong, suppuration and abscess form and a fistula tract to the skin may develop.
  - Acute severe infections of third or fourth branchial cleft cysts can cause pharyngeal edema and airway and swallowing problems.
  - Recurrent infections may complicate surgical removal, increasing the risk of injury to important structures such as the facial nerve when the parotid is involved.

- Treatment:
  - Management of branchial cleft cysts begins with controlling infection, if present, by giving antibiotics. Once the infection has resolved, the mass is usually excised surgically to prevent future problems.
  - If antibiotics are ineffective, drain the cyst and excise it surgically.

All branchial lesions should be addressed surgically

- N.B: if the cyst was treated with incision and drainage without removing the whole cyst, it can recur as a **cyst** or a **fistula**.

2. **Branchial fistula:**
    - It is a tract between two epithelial surfaces (ectoderm and endoderm). It forms due to failure of growth of the second branchial arch caudally over the third and fourth arches.
    - During development, ectoderm grows and enlarges more than endoderm, so the tract will be oblique.
    - Site:
        - Anterior triangle of the neck
        - It opens on the skin at the junction between the middle and lower third of the sternocleidomastoid muscle. Then, it extends as a tract and opens posteriorly in the mouth in the supratonsillar region.
    - Age: presents directly after birth. However, sometimes, the opening is too small and cannot be noticed.
    - Differential diagnosis:
        - Folliculitis
        - Pilonidal sinus
    - Clinical presentation:
        - If patent: The mother brings her child complaining of leakage of milk through the opening in the neck
        - If the lumen of the fistula is small, it is liable for **infections**. Usually presents as a clear discharge (rarely purulent).
        - If the opening of the fistula is obstructed the discharge will not come out leading to an infection.
        - During physical examination, feel the tract of the fistula between your fingers. It feels like a firm, thin rope.
    - Treatment:
        - Surgical excision. If incomplete, recurrence is likely.
        - **Caution**: do not open the fistula using a probe. This might damage the vessels and nerves in that area.

3. **Branchial auricle:**
    - It occurs due to overproduction of mesoderm.
    - Presents as an osseous or cartilaginous protrusion after birth.

Neck masses

DIAGNOSIS

Note: Detailed history taking & physical examination is in the OSCE dossier.

❖ History:

- Age:
  - <20: congenital > infection > malignancy
  - 20-40: benign through swelling/infection/ inflammation
  - >40: malignancy until proven otherwise

- Gender: **males** are three times more likely to have a malignancy

- Occupation:
  - Gas station: carcinoma of the sinuses
  - Crowded areas: tuberculosis
  - Outdoor worker: skin carcinoma
  - Radiation: thyroid cancer

- Mass:
  - Size: if **>2 cm**, it must be investigated
  - Duration:
    - **7 days**: infection
    - **7 months:** carcinoma
    - **7 years:** congenital
  - Number: if multiple masses, think of lymphoma
  - Progression: if rapid, think of bleeding into a cyst
  - Location: anterior triangle masses are more benign than posterior triangle masses
  - Associated symptoms:
    - Pain
    - Upper respiratory tract infection
    - Fever
    - Weight loss
    - Facial nerve invasion: manifested as **bell's palsy**. An indicator of malignancy
    - 7 cardinal symptoms of malignancy:
      - Dysphagia
      - Odynophagia
      - Voice changes (hoarseness)
      - Stridor (signifies upper airway obstruction)
      - Speech disorder
      - Globus
      - Referred pain to the ear (via CNs V, IX or X)
  - Aggravating factors:
    - If the size increases with lemon or chewing think of a **submandibular obstruction**.

- Past medical history: if the patient has a history of carcinoma, it is most probably a recurrence
- Social history:
  - Smoking: important in head and neck CA. It increases the risk of recurrence
  - Alcohol
  - Travel history
  - Animal exposure
  - Skin contact
- Family history:
  - Thyroid cancer
  - MEN syndrome

❖ Physical examination:

- Inspect all mucosal and cutaneous sites to look for signs of inflammation
- Examination under anesthesia
- Indirect/fiberoptic laryngoscopy
- Examination of the mass:
  - Site/ size / shape
  - Skin overlying it: ulceration is malignancy until proven otherwise
  - Color
  - Edges
  - Consistency
  - Fluctuation
  - Transillumination

❖ Investigations:

A. Labs:

- Complete blood count (CBC) with differential
- ESR and/or C-reactive protein (CRP) to evaluate for systemic inflammation or infection
- Blood culture (for febrile patients)
- EBV or CMV serology (when adenopathy is diffuse)
- HIV serology (in patients with increased risk)
- Specific serologic tests can be ordered when there is an increased index of suspicion for disease based on exposure, history, and examination.

B. Imaging:

- Ultrasound
- Contrast CT/MRI
- PET scan in the setting of malignancy

CT is only indicated if there is a suspected deep neck space infection

C. Diagnostic procedures:

- FNA: if negative, repeat
- Triple endoscopy with biopsy (avoid excisional biopsy, except in cases of suspected lymphoma):
  - Laryngoscopy
  - Esophagoscopy
  - Bronchoscopy

Note: In pediatric patients we use ultrasound rather than CT/MRI; Less radiation, less contrast exposure & less sedation.

❖ Differential diagnosis for posterior triangle masses:

a. Solid: lymph nodes
b. Cystic:
    i. Cystic hygroma
    ii. Pharyngeal pouch
c. Pulsatile: subclavian aneurysm

? ETIOLOGY

Neck masses are divided according to etiology into:

1. **Congenital masses:** (usually cystic, swell during URTI)

❖ Midline masses:

a. **Sublingual dermoid cyst:**
   - Dermoid cysts are due to entrapment of epithelium in deeper tissue, occurring either developmentally or post-trauma. Congenital lesions are usually midline, nontender, mobile, submental neck masses. In many patients, dermoid cysts occur on the floor of the mouth or elsewhere in the mouth.
   - Dermoid cysts in the skin are lined by an epidermis that possesses various epidermal appendages (hair follicles, sweat glands and sebaceous cysts). As a rule, these appendages are fully mature.
   - They are treated by **surgical excision**.

b. **Thyroglossal cyst:**
   - **1/3 of congenital masses**. Second most common neck abnormality after lymphadenopathy.
   - Failure of obliteration of the thyroglossal duct after descent of thyroid from foramen cecum to the lower anterior part of the neck. When this happens, midline neck cysts or ectopic thyroid tissue can develop anywhere along the path of the thyroglossal duct.
   - The cyst is present from birth and usually detected during early childhood. **50% present in patients less than 20 years old.**
   - Painless, firm midline neck mass, usually near the hyoid bone. On physical examination, it moves with swallowing because it is connected to the ligament. It also moves with tongue protrusion because it is connected to the hyoid bone.
   - May cause dysphagia or neck/throat pain if the cyst enlarges
   - Ultrasound should be done preoperatively to make that this is not the only functioning thyroid tissue in the body
   -

- Complications:
  - **Infection** of the cyst with possible abscess formation
  - **Sinus tract formation** extends to the skin with persistent drainage
  - Possible **ectopic thyroid tissue** (might be the only thyroid tissue).
  - Possible **malignancy** arising from **ectopic thyroid tissue** (rarely transforms into papillary carcinoma).
- Treatment: ***sistrunk procedure*** (resection of the cyst, tract, and central part of the hyoid bone). Treat any active infection with antibiotics before surgery.

c. **Subhyoid bursa**
d. **Thymic cyst**
e. **Laryngocele**
f. **Thyroid nodule**
g. **Pretracheal lymph nodes**
h. **Teratoma**

❖ Lateral masses:

a. **Branchial cyst** (discussed previously)
b. **Carotid artery aneurysm**

c. **Carotid body tumor**
   - Carotid body tumors are **the most common paragangliomas of the skull base and neck region (60%).** These tumors develop at the carotid **bifurcation**.
   - Approximately **one-third** are inherited as part of a **genetic syndrome**.
   - They are **locally invasive**, **slow**-growing tumors that can remain **asymptomatic** for many years.
   - Carotid body tumors typically present as **painless**, gradually enlarging masses located in the upper part of the neck below the angle of the jaw. In later stages, pain, dysphagia, deficits of cranial nerves VII, IX, X, XI and XII, and hoarseness or a Horner's syndrome may result from pressure on the vagus or sympathetic nerves.
   - Physical examination discloses a rubbery non-tender mass in the lateral neck that is more freely movable in the horizontal plane than vertically, referred to as a positive ***Fontaine's*** *sign*. Carotid body tumors are often pulsatile (it can transmit the carotid pulse, or it can have a pulse on its own), and a bruit can be heard on auscultation; however, the absence of a bruit does not rule out a carotid body tumor.
   - Diagnosis is usually made based on characteristic features demonstrated on **MRI/MRA** imaging. Duplex sonography typically indicates the mass to be hypervascular, although the absence of hypervascularity does not exclude the diagnosis
   - Treated with surgical excision and preoperative embolization

d. **Laryngocele**
e. **Thyroid masses**

❖ Masses that can present as midline or lateral masses:

a. **Cystic hygroma:**
   - Lymph-filled space that arises from the embryogenic remnant of the jugular lymph sac.
   - Not a true cyst.
   - Soft, fluctuant, translucent, lobular and painless. Contains **clear fluid**.
   - Treated by excision; **high recurrence rate**.

b. **Hemangioma:**
   - Reddish-bluish compressible mass
   - Bruit on auscultation
   - Increase in size with crying/straining
   - Associated with subglottic vascular malformation
   - Grows rapidly in **the first year of life**. Slow involution starts at 18-24 months
   - 90% resolve without treatment
   - Indications for treatment:
     - Airway compression
     - Ulceration
     - Eye problem
     - Dysphagia
     - Thrombocytopenia
     - Cardiac failure
   - Treated with steroids

c. **Pharyngeal pouch:**
   - Diverticulum in the pharyngeal mucosa that bulge through a weakness in the pharyngeal constrictor muscle on the left side.
   - Common in elderly males.
   - Presents with dysphagia, halitosis, and a swelling in the neck.
   - Diagnosed by barium swallow.

d. **Lymphatic malformation:**
   - Presents as a soft, compressible, doughy mass that swells with upper respiratory tract infections.
   - Diagnosed using CT/MRI.
   - Treatment:
     - For cosmetic or symptomatic relief.
     - Complete excision is difficult due to its infiltrative nature.
     - Treated by debulking or sclerotherapy.

e. **Pharyngeal ranula:**
   - A ranula is a cystic mucosal extravasation from the sublingual salivary gland.
   - Plunging ranula: a ranula that extends through the **mylohyoid muscle**.
   - Treatment: **excision**.

2. Infective/inflammatory masses:

a. **Cervical adenitis:**
   - Inflammation of one or more lymph nodes of the neck due to viral upper respiratory tract infection.
   - Self-limited
   - Generalized lymphadenopathy

b. **Suppurative bacterial lymphadenitis:**
   - Due to bacterial infection with Staph aureus or group A streptococcus
   - Common in children
   - Treatment:
     - IV antibiotics
     - Incision and drainage if refractory to antibiotics

c. **Deep neck space infection:**
   - Caused by a dental infection, tonsillitis, trauma, or suppurative lymph nodes
   - Most common organisms are streptococcus, staphylococcus aureus, and oral anaerobic bacteria
   - If it was a neck abscess it presents with:
     - Fever
     - Acute neck swelling
     - Induration
     - Dysphagia
     - Odynophagia
     - Stridor
     - Redness and tenderness
   - Treatment:
     - IV antibiotics
     - Incision and drainage

d. **Ludwig's angina:**
   - Cellulitis of the sublingual and submandibular spaces
   - It causes compression of the lymphatics, which leads to edema and airway obstruction
   - Treatment:
     - Airway control
     - IV antibiotics

e. **Sialadenitis/sialolithiasis**

f. **Other inflammations:**
   - Sarcoidosis
   - Kawasaki's disease
   - Lower anterior midline mass (thyroiditis)

g. **Other infections:**
   - Cat scratch disease
   - Atypical mycobacteria
   - HIV (diffuse hyperplastic actinopathy)

3. Neoplastic masses:

❖ Benign:

a. **Paraganglioma:**
   - Vascular tumor that arises from parapharyngeal cells of the autonomic nervous system
   - Treated with surgical excision and preoperative embolization

b. **Lipoma**
c. **Schwannoma**
d. **Infiltrative fibromatosis**
e. **Neurofibroma**
f. **Salivary gland neoplasm**

❖ Malignant:

a. **Metaplastic squamous cell carcinoma** (most common)

b. **Lymphoma:**
   - **Hodgkin's:**
     - 85% of the cases
     - Painless cervical lymph nodes
     - Bulky matted
   - **Non-Hodgkin's:**
     - Diagnosed by surgical biopsy
     - Treated with chemotherapy and radiotherapy

c. **Thyroid CA**
d. **Adenocarcinoma**
e. **Tonsillar SCC**

- Location of the mass is suggestive of the primary site of malignancy
  - Oral cavity CA metastasizes to submandibular triangle
  - Lateral metastatic SCC metastasizes to level II and III
  - Nasopharyngeal or scalp masses metastasize to posterior triangle
  - Papillary CA metastasizes to any level of the neck

- Note supraclavicular lymph node enlargement is usually due to an infraclavicular mass. Usually from the GIT (Virchow's and scalene lymph nodes)

Thyroid

❖ Embryology:

The thyroid gland is the **first** of the body's endocrine glands to develop, on **approximately the third week (24th day) of gestation**. It is primarily derived from **endoderm**. The ventral portion of the fourth pharyngeal pouch will develop into the lateral thyroid lobes. The thyroglossal duct develops from the median bud of the pharynx. This hollow structure migrates caudally in close proximity with the developing hyoid cartilage. It reaches a position anterior to the laryngeal cartilages and attaches to the thyroid isthmus. The pyramidal lobe originates from this migration. The thyroglossal duct atrophies and closes as the foramen cecum (at the junction of the anterior two thirds and posterior third of the tongue) before birth but can remain open in some people (thyroglossal cyst). Parafollicular cells (C cells) are derived from **the neural crest** and make up approx. 0.1% of thyroid mass, (some studies suggest that they may be in fact derived from the endoderm, but the clinical implications of this is yet unknown). The production of Thyroxin starts at the **20th week of gestation**.

❖ Anatomy:

The thyroid gland normally weighs **10-20g** in normal adults. The normal thyroid gland is immediately caudal to the larynx and encircles the anterolateral portion of the trachea. The thyroid is bordered by the trachea and esophagus medially and the carotid sheath laterally. The sternocleidomastoid muscle and the three strap muscles (sternohyoid, sternothyroid, and the superior belly of the omohyoid) border the thyroid gland anteriorly and laterally. It is one of the most vascular organs of the body.

***Structures:**
The thyroid has **two lobes** that are connected by the **isthmus**. In 55% of the population we find a **pyramidal lobe**. The lobes have superior and inferior lobes. The tubercle of Zuckerkandl, a pyramidal extension of the thyroid gland, is located on the posterior aspect of each thyroid lobe and helps in identifying t**he recurrent laryngeal nerve** that usually transverses its posterior aspect. The functioning unit is the lobule, which consists of 24-40 follicles that are lined with cuboidal epithelium. Follicles are the sites where key thyroid elements function: **Thyroglobulin (TG), Tyrosine, Iodine, Thyroxine (T4),Triiodotyrosine (T3).**

***Blood supply:**
The thyroid is mainly supplied by **the right and left superior and inferior thyroid arteries**, which are branches of **the external carotid arteries and the thyrocervical trunk, respectively**. In about **3% of the population a thyroidea ima artery is found**. It arises from the aortic arch or brachiocephalic artery and courses to the inferior portion of the isthmus or inferior thyroid lobes.

***Venous drainage:**
The superior thyroid vein travels along the superior thyroid artery and later drains into the internal jugular vein. The middle thyroid vein follows a direct course laterally to the internal jugular vein. The right inferior thyroid vein passes to the right (or the left) brachiocephalic vein, while the left inferior thyroid vein drains into the left brachiocephalic vein.

***Nerve Supply:**
The right and left superior laryngeal nerves originate from the right and left vagus nerves as they exit the base of the skull. The superior laryngeal nerves have two branches each; the external and internal
The external superior laryngeal nerve is predominantly motor. It innervates the inferior constrictor and cricothyroid muscles. **Rates of injury reach up to 30% due to the nerve being closely related to the branches of the superior thyroid artery**, the internal branch is sensory to the larynx.
The right and left recurrent laryngeal nerves, which are branches of the right and left vagus nerves, provide the larynx with sensory and motor function. They innervate all muscles to the larynx except **the cricothyroid** muscle and provide motor function for vocal cord abduction and adduction.

*Important: **In case of unilateral injury of the recurrent laryngeal nerve, the patient ends up with hoarseness. Bilateral injury will result in airway obstruction. Damage of the superior laryngeal nerve causes a deeper, quieter voice**

❖ Physiology:

There are two biologically active thyroid hormones: thyroxine **(T4)** and 3,5,3'-triiodothyronine **(T3),** T3 being the more active but less abundant form. **The half-life of T4 is 7 days**, while that of **T3 is only one day**. Both have two iodine atoms on their tyrosine ring. The thyroid gland contains large quantities of **T4 and T3 incorporated in thyroglobulin**, the protein within which the hormones are both synthesized and stored. T4, which is secreted only from the thyroid, is converted to T3 mostly in the **liver and kidneys,** but may be converted in most, if not all tissues.
The hypothalamus secretes **TRH**, which in turn stimulates the pituitary gland to release **TSH**. TSH then stimulates the thyroid to produce **T3 and T4**, which will produce **a negative feedback action on the hypothalamus and pituitary.**
Other factors that **inhibit TSH** secretion include **somatostatin**, **dopamine**, and **glucocorticoids**, but the overall impact is small, their sustained increase does not lead to sustained decreases in TSH levels (only transiently); as **serum levels of T4 and T3 overcome the inhibition**.
Parafollicular cells (C-cells) secrete **calcitonin**, which regulates serum calcium and phosphate, contrary to parathyroid hormone.

❖ Main signs and symptoms:

The main signs and symptoms of thyroid pathologies are **mass effects** due to goiter (dysphagia, stridor, shortness of breath, and feeling of a lump), **signs and symptoms of hyper/hypothyroidism**,

❖ Main Investigations:

Investigations used for the thyroid gland include **TFT, ultrasound, thyroid uptake and scan, FNA and biopsy.** Uptake measures the function of the thyroid, while a scan assesses its anatomy.

Thyroid Nodule

INTRODUCTION

Definition: A thyroid nodule is a lump in the thyroid gland. They come to attention when noted by the patient or during a routine physical exam or radiological procedure.

Epidemiology: Nodules can be found in about 5% of the general population. Thyroid cancer accounts for 4 to 6.5% of all thyroid nodules. They are more common in women.

ETIOLOGY

Causes of thyroid nodules

Benign	Malignant
Multinodular (sporadic) goiter ("colloid adenoma")	Papillary carcinoma
Hashimoto's (chronic lymphocytic) thyroiditis	Follicular carcinoma
Cysts (colloid, simple, or hemorrhagic)	Minimally or widely invasive
Follicular adenomas	Oxyphilic (Hürthle cell) type
Macrofollicular adenomas	Noninvasive follicular thyroid neoplasm with papillary-like nuclear features
Microfollicular or cellular adenomas	Medullary carcinoma
Hürthle cell (oxyphil cell) adenomas	Anaplastic carcinoma
Macro- or microfollicular patterns	Primary thyroid lymphoma
	Metastatic carcinoma (breast, renal cell, others)

Most thyroid nodules represent a variety of benign diagnoses, including colloid nodules, degenerative cysts, hyperplasia, thyroiditis, or benign neoplasms.

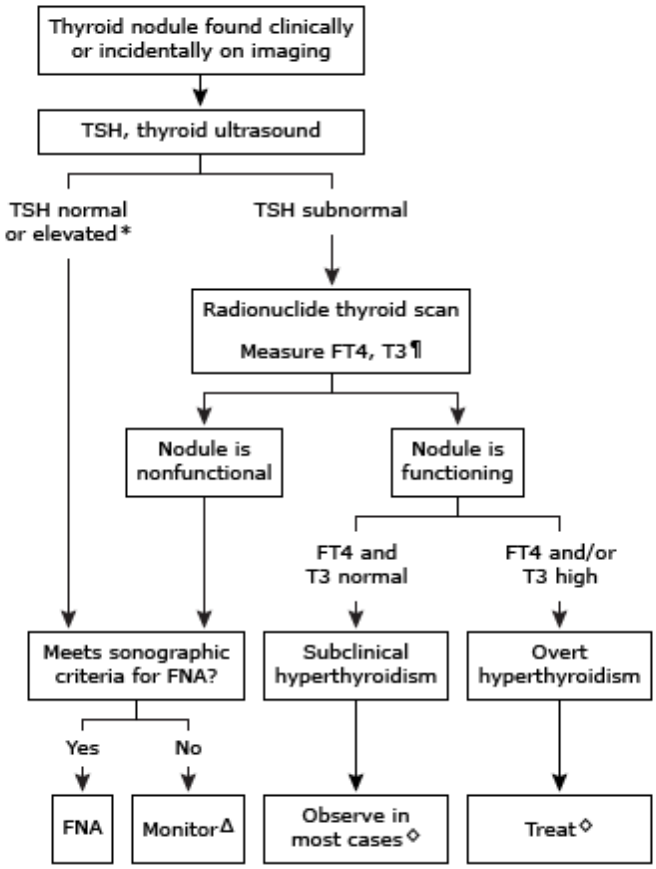
CLINICAL FEATURES

Signs and Symptoms:

The signs and symptoms of thyroid nodules depend on the underlying cause and whether the mass is causing obstruction or not.

DIAGNOSIS

Initial evaluation of a patient with a thyroid nodule



** refer to algorithm while reading the following
Initial evaluation in all patients with a thyroid nodule (discovered either by palpation or incidentally noted on a radiologic procedure) includes:

•**History and physical examination**: low accuracy for predicting cancer, however there are several features that can suggest an increased likelihood of malignancy, including **age** (<30yrs and >60yrs more likely to be cancer that 30-60yrs), **gender** (cancer rate twice as high in men), **a rapid growth** of a neck mass, childhood head and neck **irradiation**, total body irradiation for bone marrow transplantation, **family history** of thyroid cancer, or thyroid cancer **syndromes** (such as MEN 2). Physical findings of **a fixed hard mass, obstructive symptoms, cervical lymphadenopathy, or vocal cord paralysis** all suggest the possibility of cancer.

•**Measurement of serum thyroid-stimulating hormone (TSH):** If the serum TSH concentration is subnormal, indicating overt or subclinical hyperthyroidism, the possibility that the nodule is hyperfunctioning is increased and **thyroid scintigraphy** should be performed next, patients with TSH below the normal range require an evaluation for **hyperthyroidism**. If the serum TSH concentration is normal or elevated and the nodule meets sonographic criteria for sampling, then **fine-needle aspiration (FNA) biopsy is indicated**. In addition, patients with a high serum TSH concentration require an evaluation for **hypothyroidism**. Serum **TSH is an independent risk factor for predicting malignancy in a thyroid nodule.**

•**Ultrasound:** to confirm the presence of nodularity, assess sonographic features, and assess for the presence of additional nodules and lymphadenopathy. It could also provide us with information about the structures adjacent to the gland. Ultrasound should not be relied on for the diagnosis of thyroid cancer.

Ultrasound features associated with thyroid cancer risk

Ultrasonographic features that are associated with an increased risk of thyroid cancer
Hypoechoic
Microcalcifications
"Twinkling" on B-flow imaging
Central vascularity
Irregular margins
Incomplete halo
Nodule is taller than wide
Documented enlargement of a nodule
Ultrasonographic features that are associated with a low risk of thyroid cancer
Hyperechoic
Large, coarse calcifications (except medullary cancer)
Peripheral vascularity
Resembles puff or Napoleon pastry
Spongiform appearance
Comet-tail shadowing

Subsequent evaluations:

- If TSH was low or within lower portion of normal: **Thyroid scintigraphy** to determine functionality; a **nonfunctioning nodule** (uptake of radioiodine less than surrounding tissue) will **require FNA**. Hyperfunctioning nodules (uptake greater than surrounding tissue) are **rarely cancerous** so **FNA is not required**, treatment based on FT4 and T3, if high treat, if normal then it's subclinical hyperthyroidism and you should observe in most cases. Also useful in case of multiple nodules to show which are the **hypofunctional** ones that would need an FNA.
  ***Radionuclide scanning is **contraindicated** during pregnancy. Breastfeeding should also be held (the amount of time depends on isotope used)
  ***indeterminate nodules should be evaluated by FNA as most are **nonfunctioning**
- If TSH was normal or high: next step should be an **FNA-guided biopsy if nodule meets sonographic criteria for sampling.** (nodules that do not meet criteria should be monitored):
  Regardless of size:
  •Subcapsular locations adjacent to the recurrent laryngeal nerve or trachea
  •Extrathyroidal extension
  •Extrusion through rim calcifications
  •Associated with sonographically abnormal cervical lymph nodes
  FNA should be performed in nodules ≥**1 cm** (as determined by largest dimension) if they are solid and hypoechoic or have one or more of these suspicious sonographic features:
  •Irregular margins
  •Microcalcifications
  •Taller than wide shape
  •Rim calcifications

Bethesda system diagnostic categories for reporting thyroid cytopathology

Bethesda class	Diagnostic category	Cancer risk
I	Nondiagnostic (unsatisfactory)	5 to 10%
II	Benign	0 to 3%
III	Atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS)	10 to 30%
IV	Follicular neoplasm (or suspicious for follicular neoplasm)	25 to 40%
V	Suspicious for malignancy	50 to 75%
VI	Malignant	97 to 99%

HISTORY & PHYSICAL

For the history of a thyroid nodule, we should ask about its duration, progression, symptoms of the nodule (such as pain, dysphagia, etc.), associated symptoms (symptoms of hypo/hyperthyroidism), risk factors for malignancy (history of radiation or previous malignancy…), and family history.
For the physical examination, it is important to describe the nodule. We should comment on its size, site, shape, surface, color, surrounding skin, temperature, tenderness, edges, consistency, and whether or not they are fixed. Regional lymph nodes should be palpated as well.

Goiter

INTRODUCTION

Definition:

Goiter is defined as an **abnormal growth of the thyroid gland.** Goiters can be **diffuse** or **nodular**, and may be associated with normal, decreased or increased thyroid hormone production. Goiter associated with increased production of thyroid hormone is termed toxic, while goiter that is not associated with an increased production is termed non-toxic. **Most goiters are euthyroid**.

ETIOLOGY

The most common cause of goiter worldwide is **iodine deficiency**. Hashimoto's thyroiditis, multinodular goiter, and Graves' disease are common causes of goiter in adults. In older adults, multinodular goiter is most common.
Goiter may also be caused by tumors, thyroiditis, and infiltrative diseases.
Common risk factors for goiter are female gender, old age, genetic factors and family history.

PATHOPHYSIOLOGY

In patients with iodine deficiency or Hashimoto's thyroiditis, an increase in TSH secretion is the predominant cause of goiter. In contrast, most patients with sporadic nontoxic multinodular goiters have normal serum TSH concentrations. In these individuals, the thyroid enlargement is probably caused by several growth factors (including TSH) that act over time on thyroid follicular cells. Some nodules may acquire mutations within thyroid follicular cells, which result in them becoming autonomous.

CLINICAL FEATURES

Signs and symptoms depend on the growth rate of the goiter and on the presence of thyroid dysfunction. Signs and symptoms of **hyper** (multinodular goiter with autonomy or Graves' disease) or **hypothyroidism** (Hashimoto's thyroiditis or iodine deficiency) may be present. Most goiters are **asymptomatic** and may be an incidental finding. Particularly large goiters can result in **obstructive symptoms, such as exertional dyspnea, stridor, wheezing, hoarseness, and Horner's syndrome.** Pain is not common but can be brought about by sudden rapid growth causing hemorrhage. Goiter may contribute to OSA.

DIAGNOSIS

It is important to take a thorough history, focusing on family history of thyroid diseases, history of irradiation of the head and neck, presence obstructive symptoms or those of hyper- or hypothyroidism.

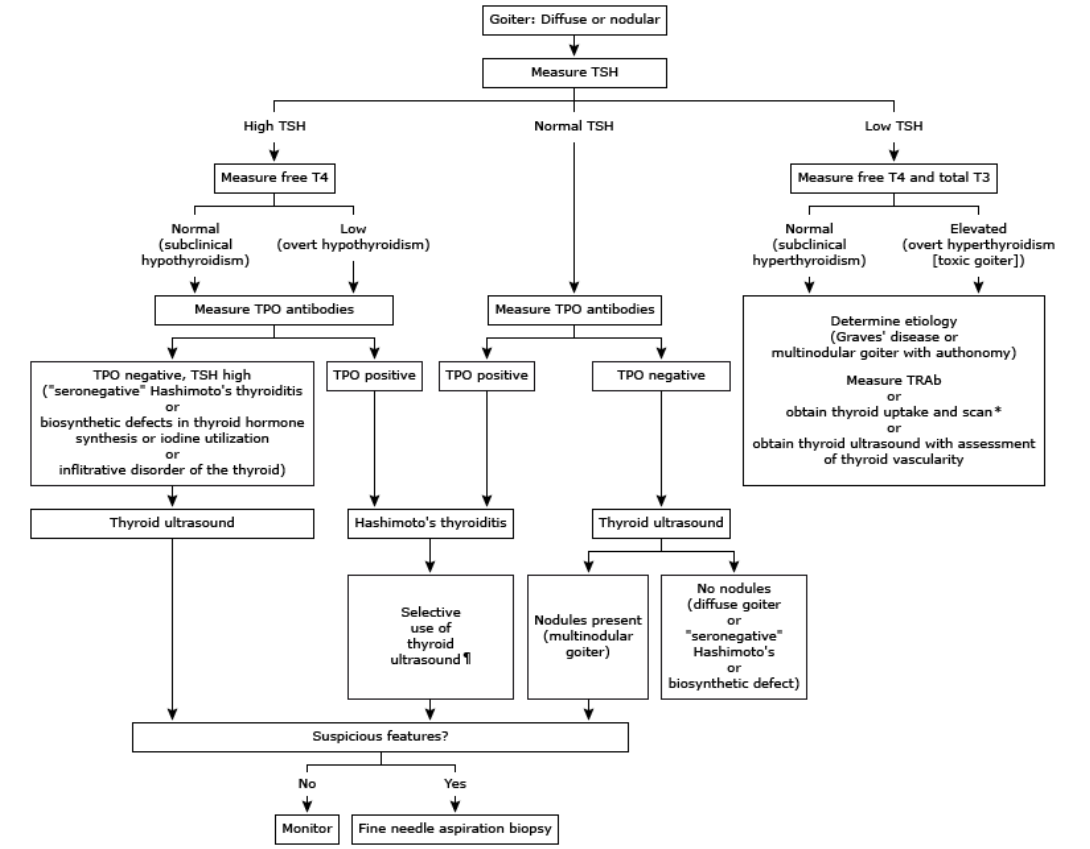
The physical exam includes assessing the size of the thyroid, presence of firm nodules and looking for asymmetry. Cervical lymph nodes should be palpated. Tracheal deviation or dilated neck veins may be present.
Initial testing is measurement of serum TSH. Ultrasound is usually done as well. Many experts measure thyroid peroxidase (TPO) antibodies to test for Hashimoto's thyroiditis.

If TSH is low, FT4 and T3 are also measured, in overt of subclinical hyperthyroidism and goiter, Multinodular goiter with autonomy and Graves' disease are at the top of the differential diagnosis, if TSH is high, T4 should be obtained. In overt or subclinical hypothyroidism, he most likely diagnosis is Hashimoto's thyroiditis (or iodine deficiency in endemic areas). Normal TSH levels can also be found in Hashimoto's thyroiditis. In this case we may do further testing, such as obtaining serum TPO antibodies

Thyroid ultrasound is done in most patients except those with low TSH and clinical features suggesting Graves' disease. Ultrasound is especially in patients who report rapid goiter growth and obstructive symptoms, those features are suggestive of malignancy, and could also occur in patients with infectious or subacute thyroiditis. When worrisome features are present on physical examination or ultrasound, FNA biopsy is indicated.

Refer to algorithm for additional tests

Evaluation of goiter in adults without obstructive symptoms



TSH: thyroid-stimulating hormone; T4: thyroxine; T3: triiodothyronine; TPO: thyroid peroxidase; TRAb: TSH-receptor antibodies.
* Focal areas of possible nodularity on thyroid scan (or exam) should be evaluated with ultrasound.
¶ We do not routinely obtain a thyroid ultrasound in patients with Hashimoto's thyroiditis. Ultrasound should be reserved for such patients with larger goiters, thyroid asymmetry, or a concern for thyroid nodularity.

TREATMENT

The treatment of goiter depends on whether it is toxic or nontoxic.
For patients diagnosed with benign nontoxic goiter (multinodular goiter, Hashimoto's thyroiditis or iodine deficiency goiter) underlying hypothyroidism must be corrected, if present with thyroid hormone replacement therapy. This alone, in some cases, may reduce the size of the goiter. We may continue with observation only. In many cases, however, the goiter does not resolve completely, and additional therapy is required.
Thyroidectomy is indicated in case of obstructive symptoms or cosmetic reasons. Surgery is also indicated if malignancy is suspected. Total or near-total thyroidectomy is the preferred procedure. In near-total thyroidectomy, both lobes of the thyroid are removed and only a small part of the thyroid is left (less than 1 mL).
Patients who are not fit for surgery, or those who refuse surgery, can benefit from radioiodine therapy.
Patients with toxic multinodular goiter (Plummer disease) or toxic adenoma, get symptomatic relief from beta blockers. To treat the excessive thyroid hormone production, surgery or radioiodine can be used. Surgery is preferred in patients who have large goiters, obstructive signs, or coexisting thyroid cancer.

Thyroid Cancer

INTRODUCTION

The prevalence of thyroid cancer has increased in both genders and all ethnic backgrounds in recent years. The annual incidence is about 0.6 million of the population.

ETIOLOGY

Most primary thyroid malignancies are derived from **follicular epithelial cells**. These tumors can be divided into differentiated (papillary, follicular) and undifferentiated (anaplastic). Parafollicular C cells can also become malignant; examples of this include **medullary carcinoma and lymphoma**. The thyroid can also be involved by metastases (most commonly from **renal cell carcinoma**).

The single most important etiological factor in differentiated thyroid carcinoma, particularly papillary, is **irradiation** of the thyroid **under five** years of age.

Malignant lymphomas sometimes develop in autoimmune thyroiditis, and the lymphatic infiltration in the autoimmune process may be an etiological factor

Other risk factors of thyroid malignancies include female gender, family history of thyroid cancer or a thyroid cancer syndrome like MEN 2 or Cowden syndrome in a first-degree relative.
Remember: Thyroid cancer is more common in females, but if a nodule is found in a male, there is a higher chance that it is malignant.

PATHOPHYSIOLOGY

[Not that important]

1. Papillary Adenocarcinoma:
   Mutations in the genes encoding for the proteins in the MAPK pathway, like RET/PTC or BRAF
2. Follicular Adenocarcinoma:
   Monoclonal origin including RAS mutations, PAX-PPAR gamma 1or others, but rarely with RET/PTC or BRAF.
   Follicular thyroid cancer can be a part of familial neoplastic syndromes like Cowden (PTEN).
4. Medullary Carcinoma:
   A neuroendocrine tumor of the parafollicular or C cells of the thyroid gland. Most are sporadic but approximately 25% are familial as part of MEN2 (RET proto-oncogene)
5. Anaplastic Carcinoma:Undifferentiated tumors of the thyroid follicular epithelium. Some studies suggest that it arises from well-differentiated thyroid cancers that have accumulated a huge amount of mutations. These cancers arise form RAS-mutation positive differentiated cancers.

CLINICAL FEATURES

The most common presenting symptom is **thyroid swelling**. Enlarged cervical lymph nodes can be the presenting symptom of papillary carcinoma. **Recurrent laryngeal nerve paralysis is very suggestive of locally advanced disease.**
Constitutional symptoms can be seen, which include **fever of unknown origin, anorexia, weight loss and fatigue.**
Anaplastic growths are usually hard, irregular and infiltrating. A differentiated carcinoma may be suspiciously firm and irregular but is often indistinguishable from a benign swelling. Small papillary tumours may be impalpable, even when lymphatic metastases are present. Pain, often referred to the ear, is suggestive of nerve involvement from infiltrating tumors.
The most common type of thyroid cancer is papillary adenocarcinoma, accounting for up to 80% of all thyroid cancers. The average age at diagnosis is rather young; 30 to 40 years.
The prognosis is excellent, with a 10-year survival rate above 95%. About 50% of papillary cancers are found to have psammoma bodies, which are round calcifications. This type of thyroid cancer most commonly spreads via the lymphatics, and positive cervical lymph nodes do not affect the prognosis. The most common site for distant metastasis is the lung. Thyroglobulin is a tumor marker for this type of cancer.

Follicular adenocarcinoma is the second most common type, comprising for about 10% of thyroid cancers. Blood borne metastasis is more common than it is for papillary thyroid cancer. It is more aggressive than papillary cancer and has a higher mortality rate, but overall still excellent compared to most cancers Follicular type will most commonly spread to the bone with lytic lesions.

- Hürthle cell cancer was considered a variant of follicular thyroid cancer but recent studies indicate that it is a distinct tumor type (some sources and doctors will still consider it follicular cell variant), it has a similar clinical presentation as follicular, but unlike follicular carcinoma it commonly spreads to lymph nodes, has poor radioactive iodine uptake and a worse prognosis, it is less common than the previously mentioned types, making up only 5% of thyroid cancers.

Medullary carcinoma is as common as Hürthle cell thyroid cancer, accounting for 5% of thyroid cancers. The prognosis depends on whether or not lymph nodes are involved. The male to female ratio is 1:1.5. The 10-year survival rate without lymph node involvement is about 80%, while it is only 45% with lymph node involvement. It spreads via lymphatics and hematogenously. It commonly spreads to liver, lung and bone. High levels of serum calcitonin and carcinoembryonic antigen are produced by many medullary tumors. Therefore, calcitonin can be used for patient follow up, as levels fall after resection of the tumor. On histology, medullary carcinoma shows a characteristic amyloid stroma.
In about 10-20% of cases medullary carcinoma is familial, presenting as part of multiple endocrine neoplasia type 2A (Medullary carcinoma, adrenal pheochromocytoma, hyperparathyroidism).

Anaplastic carcinoma is one of the most aggressive cancers in humans. It makes up 2% of thyroid cancers. The prognosis is dismal; disease specific mortality approaches 100%. Almost all patients die within six months. In most cases, distant spread is apparent at time of diagnosis, most commonly found in the lungs.

Evaluation and work up of thyroid nodules have already been discussed.
It is essential to take a complete history and perform an adequate physical exam on the patient. As previously mentioned, family history and radiation exposure are very important. Regional lymph nodes should be palpated, and thyroid function should be assessed.
Ultrasound should be performed to look for suspicious features. For suspicious or indeterminate lesions, fine needle aspiration is performed. If medullary thyroid cancer is suspected, calcitonin levels may be obtained by doing the pentagastrin-stimulated calcitonin test.
In thyrotoxic patients, radioiodine uptake scan is done. Cold nodules require further assessment, such as FNA.
For follicular adenocarcinoma, FNA alone is not sufficient, as it is hard to distinguish from benign follicular adenoma just by histology. For this reason, tissue structure is needed for an accurate diagnosis.

Papillary adenocarcinoma and follicular adenocarcinoma are both differentiated tumors, therefore they are treated in a similar fashion. Prior to surgery, patients should be evaluated by ultrasound. The surgery of choice depends on the extent of the disease and patient's factors such as age and other comorbidities.
For tumors <1 cm without extrathyroidal extension and negative lymph nodes, lobectomy is preferred. The contralateral lobe may be removed if it is suspicious for cancer, or if the patient has strong family history for thyroid cancer.
Tumors sized 1 to 4 cm without extrathyroidal extension and no lymph nodes, thyroidectomy or lobectomy, depending on ultrasound findings or preference of the patient.
Tumors ≥4 cm with extrathyroidal extension or metastases should go for total thyroidectomy. Neck dissection should be considered as well in case of nodal metastasis. Depending on site of involvement, either central or lateral neck dissection is performed.
For patients who underwent head and neck radiation during childhood, total thyroidectomy is recommended regardless of tumor size.
In high risk patients, radioactive iodine therapy is recommended. Multiple doses may also be given in case of unresectable disease or distant metastasis.
Hürthle cell thyroid cancer is most commonly treated by total thyroidectomy.
For medullary carcinoma, total thyroidectomy is recommended in addition to elective central neck dissection.
Treatment of anaplastic carcinoma is less straightforward. In case of resectable tumors, total thyroidectomy in addition to radiotherapy and chemotherapy is suggested. If disease is advanced, radiotherapy and chemotherapy may still be used. For metastatic disease, there is no cure. The patient's airway should be secured by tracheostomy. Palliative radiotherapy for metastatic disease may be beneficial in reducing pain.

Complications of thyroid surgery:

- Hemorrhage: Occurs about 6 hours postoperatively. Presents as postoperative shortness of breath. (Remember: postoperative shortness of breath can be due bilateral recurrent laryngeal nerve injury or due to a hematoma.) Management: ABC, then hematoma evacuation
- Hypocalcemia: It is usually transient, due to parathyroid blood supply compromise. As a prophylactic measurement, parts of the parathyroid gland are taken and autografted into the sternocleidomastoid or in the forearm.
- Recurrent laryngeal nerve injury: 1%

Hyperthyroidism

Hyperthyroidism consists of multiple disorders that present with excessive synthesis of thyroid hormones, leading to **thyrotoxicosis**.

Risk factors for developing hyperthyroidism include family history, particularly of Graves' disease, female sex, and personal history of other autoimmune disorders such as pernicious anemia and diabetes mellitus type 1

Clinical types of hyperthyroidism are: diffuse toxic goiter (Graves' disease), toxic nodular goiter, toxic nodule, other rare causes.
Graves' disease is usually seen in young women. It is the most common cause of hyperthyroidism. About 50% of patients have family history of endocrine autoimmune disease. It is caused by circulating antibodies that activate TSH receptors on follicular cells. This leads to deregulated production of thyroid hormone.
Toxic nodular goiter is seen in middle-aged or elderly women. Many times, the nodules are inactive, and the remaining thyroid tissue is what is causing the hyperthyroidism.
Toxic nodule is a single overactive nodule. This nodule may be a toxic adenoma or a part of multiple nodules whose functional capacity is independent of regulation by TSH. The thyroid tissue surrounding this nodule is usually inactive as it is suppressed.

CLINICAL FEATURES

Patients with hyperthyroidism may present with **warm** (rarely erythematous) **skin**, **increased sweating and heat intolerance, hyperpigmentation** (in severe cases), **pruritus** (primarily in patients with Graves), **oncholysis**, and **thinning of the hair**. **Vitiligo** and **alopecia areata** can occur in association with autoimmune disorders. **Lid lag is seen in all patients with hyperthyroidism**. The patient may also note **diplopia**, corneal ulceration due to the **proptosis**. Cardiovascular manifestations include **increased heart rate, systolic hypertension and wide pulse pressure, and atrial fibrillation. anxiety, emotional lability, weakness, tremor, palpitations, Dyspnea on exertion, weight loss**
with hyperphagia, hyperdefecation, and clubbing (thyroid acropachy), urinary frequency, oligomenorrhea or amenorrhea in women, and gynecomastia and erectile dysfunction in men are also common. Other conditions that should suggest the possibility of hyperthyroidism include osteoporosis, hypercalcemia, heart failure, premature atrial contractions, shortness of breath, and a deterioration in glycemic control in patients with previously diagnosed diabetes. Clinical features that are specific to Graves' disease are thyroid ophthalmopathy (characterized by inflamed extraocular muscles and orbital fat and connective tissue, impaired eye muscle function and periorbital edema) and pretibial myxedema.

DIAGNOSIS

The previously stated signs and symptoms may be noted during history and physical examination. The next step is to do a thyroid function test. Low serum TSH and high free T4/T3 is seen in primary hyperthyroidism. After this, we must find the underlying cause of hyperthyroidism. Lab tests that are usually done are thyrotropin receptor antibodies, radioactive iodine uptake, and measurement of thyroidal blood flow on ultrasonography.
Remember that radioactive iodine is contraindicated in pregnancy.
If TRAb are positive, the diagnosis is Graves' disease. Radioactive iodine uptake can help us differentiate Graves' disease from other causes of hyperthyroidism. A toxic adenoma will be seen as a focal increase in uptake, toxic multinodular goiter appears as multiple areas of focal increased with areas of suppressed uptake, and Graves' disease appears as a diffuse increase in uptake.

TREATMENT

Antithyroid drugs such as propylthiouracil can help restore the euthyroid state of the patient. The production of TRAb may cease. However, they are not useful for toxic nodules, as hyperthyroidism will recur as soon as the drug is stopped.
For diffuse toxic goiter and toxic nodular goiter, subtotal thyroidectomy is beneficial in restoring a euthyroid state. However, recurrence is still possible.
Radioiodine can beneficial to the patient, as it reduces the mass of functioning thyroid tissue. Eye signs may be aggravated by radioiodine therapy. One of the complications is post-treatment hypothyroidism. It is contraindicated in pregnancy.

Hypothyroidism

ETIOLOGY

There are numerous causes for hypothyroidism. Iodine insufficiency is the most common cause in deficient areas. Hashimoto's thyroiditis is the most common cause in areas with sufficient iodine. It is a chronic autoimmune destructive lymphocytic infiltration of the thyroid. Reidel's thyroiditis is another chronic cause of hypothyroidism. It's a benign progressive inflammatory thyroid enlargement with fibrosis that presents as an enlarged painless thyroid. Hypothyroidism may be a result of over treating hyperthyroidism or of thyroid surgery or acute suppurative thyroiditis by strep or staph infection/

CLINICAL FEATURES

Hypothyroidism may be asymptomatic, but commonly manifests as slowed mental and physical activity. The patients may complain of fatigue, weight gain despite decreased appetite, cold intolerance, joint pain, depression, emotional lability, constipation, blurred vision, hoarseness, dry skin, thinning of hair, and menorrhagia in females.

Since signs and symptoms are usually inconclusive in hypothyroidism, we rely heavily on investigations. High serum TSH and low free T4 are indicative of primary hypothyroidism, which makes up about 95% of hypothyroidism cases. Central hypothyroidism is diagnosed by low serum T4 and TSH that isn't appropriately elevated. Serum thyroid peroxidase (TPO) antibodies are not routinely measured, as most hypothyroidism patients have Hashimoto. They are found to be elevated in over 90% of Hashimoto patients.

The preferred treatment for hypothyroidism is synthetic thyroxine (T4). Surgery may be indicated to reduce goiter size if it's too large and causes discomfort in Hashimoto's thyroiditis.

Parathyroid

⁂ **Embryology:** The four parathyroid glands, like the thymus, arise from endodermal epithelial cells. They develop between the fifth and twelfth week of gestation. The fourth branchial pouch gives rise to the superior parathyroid glands. The third branchial pouch gives rise to the inferior parathyroid glands. Since these glands have a longer descent, variations in position are more likely. The inferior glands are closely associated with the thymus and the inferior thyroid pole. Ectopic parathyroid glands may be found anywhere along the common origins of the parathyroid, thyroid and thymus. About 10% of the population are found to have 3 glands, 5% have 5 glands.

⁂ **Anatomy:** The normal parathyroid glands weigh about 35-50 milligrams. Their color can vary from light yellow to brown red. They are most commonly oval, spherical or bean shaped. They are located at the postero-lateral aspect of the thyroid gland. The superior glands are found on the junction between the upper third and lower two thirds at the posterior aspect of the thyroid. They are posterior to the recurrent laryngeal nerve. The inferior glands are anterior to the recurrent laryngeal nerve.

Blood supply: Both the superior and inferior glands are supplied by the inferior thyroidal artery. In about 20% of the population, the superior glands are supplied by the superior thyroidal artery.

Venous drainage: The parathyroid glands' venous drainage comes from the superior, middle and inferior thyroid veins, which then drain into the internal jugular vein or the innominate vein.

Nerve supply: The nerve supply is usually directly from superior or middle cervical ganglia.

⁂ **Physiology:** There are two types of cells in the parathyroid glands. Chief cells are the more predominant cell type. They are responsible for production and secretion of PTH in response to low calcium levels or high magnesium levels. Oxyphil cells are larger and scattered in between chief cells. Their function is unknown. They may secrete PTH in cases of hyperparathyroidism.

The major function of PTH, an 84 amino acid peptide, is to increase the calcium levels, but it also decreases serum phosphate. It does this by increased calcium absorption, phosphate excretion and increased hydroxylation of 25-hydroxyvitamin D in the kidneys, increased calcium absorption in the GIT (duodenum and proximal

jejunum) and bone breakdown. It has a half-life of about 4 minutes. The active form of Vitamin D (1,25-dihydroxyvitamin D) in turn increases the absorption of calcium as well as phosphate in the intestine.

The functions of calcium in the body include contraction of muscles and secretion of glands, neuromuscular junction conduction, acting as a second messenger and coenzyme, and functioning in blood coagulation. About 40% of calcium in serum is bound to albumin, 50% is free and 10% is bound to phosphate and citrate.

⁂ **Main signs and symptoms:** Signs and symptoms of parathyroid pathology are usually vague. Most common signs and symptoms include kidney stones, abdominal pain, pathological fractures, osteoporosis, muscle pain, and anxiety. Other symptoms that are even less specific are weight loss, weakness, constipation, and anorexia.

⁂ **Main Investigations:** Common investigations for parathyroid pathologies are serum levels of PTH, calcium, phosphorous, magnesium. Urine calcium is also useful. For imaging, ultrasound, sestamibi scan, CT scan, or MRI scan may be used.

Hyperparathyroidism

INTRODUCTION

Definition: Hyperparathyroidism is defined as excessive secretion of **PTH**.

ETIOLOGY

Primary hyperparathyroidism: In most cases, primary hyperparathyroidism is caused by one single adenoma. However multiple adenomas may be found as well. Hyperplasia or cancer of the parathyroid glands can cause hyperparathyroidism too. Parathyroid carcinoma, which is a rare cause of primary hyperparathyroidism (1%), usually affects a single gland. Risk factors for this type of hyperparathyroidism include family history and MEN 1 and MEN 2A, and irradiation.

Secondary hyperparathyroidism: Chronic kidney disease is the most common cause of secondary hyperparathyroidism. Vitamin D deficiency, intestinal malabsorption of calcium and liver disease are other causes.

Tertiary hyperparathyroidism: Non-suppressible PTH secretion and slow involution of enlarged glands are causes for tertiary hyperparathyroidism.

PATHOPHYSIOLOGY

As mentioned briefly above, there are three types of hyperparathyroidism; primary, secondary, and tertiary. Primary hyperparathyroidism caused by **adenomas** results in loss of normal feedback on PTH by extracellular calcium. In parathyroid hyperplasia, the increase in the number of cells producing PTH is the most likely cause. Secondary hyperparathyroidism due to **chronic kidney disease** results from **calcium wasting**. Tertiary hyperparathyroidism is **persistent excess secretion of PTH after correction of secondary hyperparathyroidism due to loss of the negative feedback of calcium.**

CLINICAL FEATURES

Signs and Symptoms:

- Most commonly **asymptomatic**
- Signs and symptoms of primary hyperparathyroidism that can be seen may be remembered by "**stones, bones, groans and psychiatric moans**."
- Kidney stones
- Bone pain, osteoporosis, pathological fractures
- Muscle pain and weakness
- Pancreatitis
- Constipation
- Nausea and vomiting
- Coma
- Depression and anxiety
- Anorexia and weight loss
- Hypertension
- Polyuria and Polydipsia
- Lethargy
- Symptoms are usually due to hypercalcemia itself. Increases in calcium levels may cause increased gastric acid secretion, making patients more susceptible to peptic ulcer disease.
- A palpable parathyroid gland, a painful neck, recurrent laryngeal nerve paralysis may be signs of malignancy.
- Secondary hyperparathyroidism is often incidentally discovered on routine lab tests for chronic kidney disease patients. In these cases, there is often no unique clinical presentation. Patients with secondary hyperparathyroidism due to

Vitamin D deficiency develop symptoms that are due to the vitamin deficiency, such as increased fracture risk or bone pain.

- Tertiary hyperparathyroidism manifests by the effects of hypercalcemia and hyperphosphatemia. The patients may note fatigue, lethargy, and bone pain.

Primary hyperparathyroidism is a biochemical diagnosis. We must confirm it by elevated serum calcium concentrations and elevated **PTH** concentration; we may also test **for serum phosphate levels**, which will be **low**. Vitamin D levels as well as creatinine are usually normal, and 24-hour calcium excretion may be normal or elevated. If malignancy is suspected, we may obtain human chorionic gonadotropin, as it is a tumor marker for parathyroid carcinoma.

If PTH is only slightly elevated or within the normal range, familial hypocalciuric hypercalcemia (explained later) may be a differential diagnosis. To rule this out, we do a 24 hour urinary collection.

After biochemical testing, we may go for imaging if a surgery is planned. Sestamibi scanning is the most accurate imaging method for the parathyroid glands. It is safe. Sestamibi accumulates in mitochondria and later washes out at different speeds, depending on the amount of mitochondria within tissues. Parathyroid adenomas have high mitochondrial content and therefore have slow washout. Ultrasound is another imaging method used. Parathyroid adenomas appear oval or elongated and hyperechoic. Other imaging methods used are MRI, CT, and more rarely parathyroid angiography and venous PTH sampling. If X-rays are done, subperiosteal bone resorption may be found, typically in the hands.

If secondary hyperparathyroidism is suspected, PTH, calcium, phosphorous and 25-hydroxyvitamin should be measured. Calcium levels are typically low to normal, PTH is elevated, phosphate levels are elevated and vitamin D deficiency is evident. Imaging of the parathyroid glands is not indicated unless primary hyperparathyroidism is suspected.

Tertiary hyperparathyroidism is difficult to distinguish from primary hyperparathyroidism. Calcium and PTH levels are elevated.

The mainstay of primary hyperparathyroidism treatment is surgery. If a single adenoma was confirmed by imaging, minimally invasive parathyroidectomy is done. Where imaging fails to identify abnormalities, bilateral neck exploration is

performed. If hyperplasia is discovered, a four-gland parathyroidectomy is performed and at least 30 mg of parathyroid tissue is placed into the patient's forearm. In case of carcinoma, we remove the tumor and the ipsilateral thyroid lobe in addition to enlarged lymph nodes.

Secondary hyperparathyroidism is most commonly treated by medical therapy. Replacement of calcium, vitamin D and reduction of phosphate by phosphate binders are considered standard management. A new class of drugs that reduces PTH levels by binding to and activating calcium sensing receptors, known as calcimimetics, are also used. For chronic kidney disease patients, renal replacement remains the only definite treatment. Parathyroidectomy may be performed in case of hyperphosphatemia and hypercalcemia refractive to medical treatment, and severely impaired quality of life.

The definite treatment of tertiary hyperparathyroidism is surgery.

Parathyroidectomy may be complicated by recurrent or superior laryngeal nerve injury, permanent hypoparathyroidism and post-operative hypocalcemia, persistent or recurrent hyperparathyroidism, and neck hematoma. Signs and symptoms of hypocalcemia include perioral numbness, paresthesia, tetany, Chovstek's sign, and Trousseau's sign.

Indications of surgery in asymptomatic hyperparathyroidism:

- Age <50
- Patients who cannot get appropriate follow up
- Serum Ca >1mg above normal range
- Urine Ca >400mg (obsolete criterion)
- 30% decrease in creatinine clearance
- Complications of hyperparahyroidism including nephrocalcinosis and osteofibrosis

Note: The most common cause of hypercalcemia in hospitalized patients is **cancer**, while the most common cause of hypercalcemia in outpatients is **hyperparathyroidism**.

DDx of hypercalcemia: CHIMPANZEES

1) **C**alcium overdose
2) **H**yperparathyroidism
3) **I**mmobility/iatrogenic
4) **M**etastasis/milk alkali syndrome
5) **P**aget's disease
6) **A**ddison's/acromegaly
7) **N**eoplasm
8) **Z**ollinger Ellison syndrome
9) **E**xcessive vitamin A
10) **E**xcessive vitamin D
11) **S**arcoidosis

Familial hypocalciuric hypercalcemia

FHH is a condition of autosomal dominant inheritance, resulting from a mutation in calcium sensing receptors leading to loss of feedback inhibition. It is characterized by mild hypercalcemia in a young asymptomatic patient. These patients have a normal or slightly elevated PTH, increased serum magnesium and hypocalciuria.

To differentiate between primary hyperparathyroidism and FHH, we obtain a **urinary calcium/creatinine clearance ratio (24 hour urine collection).** In FHH this ratio will be low. Patients usually don't need any medical or surgical interventions.

Pancreas

⁂ Embryology:

During the **4th** week of gestation, the pancreas begins to develop from the **duodenal endoderm**. Two buds form (which then rotate and fuse by the 8th week):

VENTRAL BUD (from the convex part of the duodenum) →Uncinate process and part of the head

DORSAL BUD (from the concave part of the duodenum) → Remaining part of the head, neck, body and tail.

The ventral bud rotates with the duodenum and then migrates posteriorly to fuse with the dorsal part. The ventral duct (the bud's duct) will take over and open into the duodenum at the ampulla of Vater →Wirsung duct (main pancreatic duct).

The dorsal duct may persist and opens into the the duodenum at a minor opening 2 cm medial and above the ampulla of Vater, BUT it usually disappears → Santorini duct.

At the 3rd- 4th month, islets of Langerhans appear and become active.

⁂ Anatomy:

- A retroperitoneal organ.
- Divided into head, uncinate process, neck, body and tail.
- The head is within the curve of the duodenum. Posterior to it are the vena cava and 2nd lumbar vertebra.
- The neck lies anterior to the aorta and superior mesenteric vessels.
- The portal vein forms behind the neck of the pancreas, by the joining of the splenic and superior mesenteric vein.
- The tail extends to the hilum of the spleen.
- The pancreas weighs about 85 g.
- Clusters of endocrine cells, called islet of Langerhans are distributed all over the pancreas. Islets are made of various types of cells: 75% Beta cells (produce insulin and C-peptide) and 20% Alpha cells (produce glucagon). The remaining cells are Delta cells (produce somatostatin) and pancreatic polypeptide cells (produce vasoactive intestinal peptide).

Blood supply:

- ❖ The head of the pancreas is supplied by the Anterior superior pancreaticoduodenal artery and the posterior superior pancreaticoduodenal artery (branches of the gastroduodenal artery, which comes from the celiac trunk) as well as the anterior inferior pancreaticoduodenal and posterior inferior pancreaticoduodenal arteries (branches of the superior mesenteric artery).
- ❖ The rest of the pancreas is supplied by the dorsal pancreatic artery, a branch of the splenic artery.

(The venous drainage follows the arterial supply.)

Nerve supply:

- Parasympathetic nerve supply → posterior vagal trunk via the celiac branch.
- Sympathetic nerve supply (pain sensation) → thoracic splanchnic nerves and the celiac plexus.

⁂ Physiology:

- Glucagon, secreted by the alpha cells, is regulated by the blood glucose concentration. When blood glucose is decreased or blood amino acids increased, secretion of glucagon is stimulated. Glucagon is responsible for increasing the blood glucose concentration. It does this by acting on the liver and adipose tissue, increasing glycogenolysis and gluconeogenesis. Other effects of glucagon are increasing lipolysis and urea production.

- Insulin, which is secreted by the beta cells, is regulated by the blood glucose concentration as well. In the case of increased blood glucose, insulin is secreted. The effects of insulin are mainly on the liver, muscle and adipose tissue. Insulin is responsible for lowering the blood glucose concentrations and it does so by increasing the uptake of glucose into target cells that have glucose transporters in their cell membrane. In the muscle and liver glucose is incorporated into glycogen, while glycogenolysis is inhibited. Another way insulin decreases the blood concentration of glucose is by decreasing gluconeogenesis. Other actions of insulin include decreased blood fatty acids, amino acid concentration and potassium ions.

- Delta cells are responsible for the secretion of somatostatin, which in turn inhibits secretion of gastrin, insulin, glucagon, and small bowel electrolytes.

- Polypeptide cells secrete vasoactive intestinal polypeptide (VIP), which is also released by other organs of the GIT. VIP acts to produce relaxation of the smooth muscles in the GIT, one example being the lower esophageal sphincter.

Pancreatic Endocrine Tumors

INTRODUCTION

Definition: Pancreatic endocrine tumors, also known as islet cell tumors, are a rare type of neoplasm. They arise from the endocrine tissues of the pancreas.

Epidemiology: Pancreatic endocrine tumors make up 5% of clinically detected pancreatic tumors. They may be single or multiple, benign or malignant. All of these tumors are usually malignant, except for insulinomas.

ETIOLOGY

Pancreatic endocrine tumors can be functional, producing specific symptoms of the hormones released, or non-functional (50-75% of cases), presenting similar to pancreatic adenocarcinoma. In 10-20% of cases, they are associated with MEN 1.

In most cases, these neoplasms are sporadic, but in some cases they are associated with hereditary syndromes, such as MEN1 (10-20% of cases), von Hippel-Lindau syndrome, and neurofibromatosis type. About 80-100% of MEN1 patients, 20% of VHL patients and 10% of NF1 patients develop a pancreatic endocrine tumor.

These tumors can become apparent at any age, but most commonly do so between the fourth and sixth decades of life. Potential risk factors for pancreatic endocrine tumors are smoking, diabetes and history of chronic pancreatitis.

Insulinoma

INTRODUCTION

Definition: An insulinoma is a type of pancreatic endocrine tumor that produces insulin.

Epidemiology: Insulinomas are the most frequent type of functioning pancreatic endocrine tumors. Their incidence is about 2-4 cases per million per year. Women are slightly more likely to be affected than men.

ETIOLOGY

There are no known risk factors for this type of pancreatic endocrine tumor and its etiology is unknown.

PATHOPHYSIOLOGY

The pathogenesis of insulinomas is currently unknown.

CLINICAL FEATURES

Patients with an insulinoma commonly present with fasting hypoglycemia symptoms (Whipple's triad: hypoglycemic syndromes, blood glucose <50 mg/dL during attack and symptoms relived by IV glucose) and neuroglycopenic symptoms including diplopia, blurred vision, abnormal behavior and amnesia. The secretion of catecholamines results in sweating, weakness, tremor, anxiety, tachycardia, hunger, anxiety and palpitations.

DIAGNOSIS

- It can be difficult to distinguish insulinomas from other causes of hypoglycemia such as hormonal deficiencies, hepatic insufficiency and medications.
- The most sensitive test is a fasting test, in which insulin, proinsulin, C-peptide and blood glucose are measured in 1 to 2 hour intervals. The diagnosis can be established if inappropriately high insulin concentrations are found as well as increased levels of C peptide and proinsulin during hypoglycemia.
- Elevated C-peptide can help exclude factitious hypoglycemia, which is caused by insulin injections.
- After diagnosis of insulinoma, imaging techniques are used. Transabdominal ultrasound is the preferred initial test. CT and MRI may be used as well.
- Endoscopic ultrasound and selective arterial calcium stimulation are more invasive imaging modalities.

TREATMENT

Medical treatment is used if the patient is unfit for surgery or disease is unresectable. Diazoxide directly acts on beta cells and suppresses insulin secretion. Chemotherapy may be another option.

All patients should be advised to undergo surgical excision of the insulinoma. Some of the options available are enucleation of the insulinoma (removing only tumor cells), debulking of the tumor (removing only part of the tumor, as the rest passes through important structures), partial distal pancreatectomy, and whipple procedure. The procedure of choice depends on extent of tumor extension.

The most prevalent complication after insulinoma resection is hyperglycemia. It usually persists for the first 48-72 hours after surgery. If glucose levels are above 300 mg/dL subcutaneous insulin may become necessary. Patients that underwent major pancreatic resections may develop diabetes, for this reason, we sometimes begin with medical treatment before going for the surgery.

Gastrinoma (Zollinger-Ellison Syndrome)

INTRODUCTION

Definition: A gastrinoma is a gastrin-secreting tumor that can occur in the pancreas, although it is most commonly found in the duodenum. Zollinger-Ellison syndrome is a condition that includes non-beta islet cell pancreas tumors (gastrinoma), recurrent ulcers in the stomach duodenum or atypical sites despite adequate treatment.

Epidemiology: Gastrinomas are the second most common type of functioning pancreatic endocrine tumors. ZES is more common in men, with a mean age of 38 at symptom onset.

ETIOLOGY

- The etiology of gastrinomas is unknown.
- More than 60% of gastrinomas are malignant.
- More than 70% of the tumors are found in the gastrinoma triangle, which is made of: cystic duct/common bile duct junction, head and neck of the pancreas, junction of the second and third part of duodenum.
- One fourth of gastrinomas are associated with MEN 1.

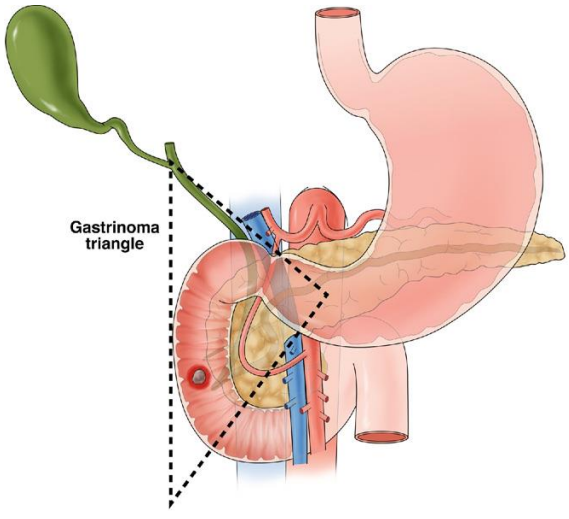


Figure 1 The Gastrinoma Triangle (of Stabile) is bound by the junction

PATHOPHYSIOLOGY

- Tumor cells secrete high amounts of gastrin, which causes hyperplasia of fundic parietal cells and results in increased acid secretion. This results in ulceration that may extend as far as the small intestine.

- Acidic contents in the small intestine stimulate secretin release, resulting in diarrhea.

CLINICAL FEATURES

Signs and Symptoms:

- More than 90% of patients have peptic ulcer disease, often multiple or at unusual sites.
- Chronic diarrhea
- Abdominal pain (seen in 75%)
- Weight loss

Complications:

- Bleeding
- Stricture formation
- Perforation

DIAGNOSIS

- The diagnosis of ZES can be confirmed by a gastric pH <2.5 and serum gastrin concentration >1000 pg/mL.
- Secretin stimulation test is used to distinguish gastrinoma from the other differentials.
- The differential diagnosis includes GERD, idiopathic peptic ulcer disease, chronic atrophic gastritis, gastric outlet stenosis and retained antrum after gastric resection.
- Imaging studies that are useful in localizing the tumor are: somatostatin receptor scintigraphy (SRS), endoscopic ultrasonography, CT and MRI.

TREATMENT

Medical:

- Gastric hypersecretion can be treated with PPI or octreotide.
- Chemotherapy is used in patients with diffuse metastases.

Surgical:

- Surgery is indicated in all patients without metastases.
- About 40% of patients end up with hyperacidity postoperatively and need prolonged antisecretory therapy.

VIPoma

- These tumors secrete vasoactive intestinal peptides.
- This type is rare.
- Thye are usually solitary.
- May be associated with MEN 1
- Symtomps :
  - ❖ Patients have VIPoma syndrome which consists of watery diarrhea that persists with fasting.
  - ❖ Symptoms related to hypokalemia and dehydration: lethargy, muscle weakness and cramps, nausea and vomiting.
  - ❖ Hypocalcemia
  - ❖ Achlorhydria/hypochlorhydria
- Diagnosis: increased VIP >75 pg/mL, decreased K+
- Symptomatic treatment consists of replacing the fluid and electrolytes that are lost and somatostatin analogues, which control diarrhea.
- Treated by resection (distal pancreatectomy, since it is usually in the dital pancreas)

Glucagonoma

- Glucagon secreting tumor, rare and usually solitary.
- Symptoms:
  - ❖ Weight loss
  - ❖ Anemia
  - ❖ Glucose intolerance/diabetes mellitus
  - ❖ Characteristic skin rash (Necrolytic migratory erythema)
  - ❖ Hypoaminoacidemia
- Diagnosed by increased plasma glucagon >500 pg/mL
- Treatment :resection

Somatostatinoma

- Rare
- D-cell tumor; secreting somatostatin
- Usually in the head of pancreas
- Clinical presentation (3D’s):
  - ❖ Diarrhea
  - ❖ Diabetes
  - ❖ Dilated gallbladder with stones

Diabetic foot

INTRODUCTION

Definition: A diabetic foot is a foot that exhibits any pathology that results directly from diabetes mellitus or any long-term (or "chronic") complication of diabetes mellitus.

Epidemiology

Diabetic foot lesions are responsible for more hospitalizations than any other complication of diabetes. Among patients with diabetes, 15% develop a foot ulcer, and 12-24% of individuals with a foot ulcer require amputation.

Diabetic neuropathy tends to occur about 10 years after the onset of diabetes, and, therefore, diabetic foot deformity and ulceration occur sometime thereafter.

Prognosis

Mortality in people with diabetes and foot ulcers is often the result of associated large vessel arteriosclerotic disease involving the coronary or renal arteries.

ETIOLOGY

1) Neuropathy

2) Arterial disease

3) Pressure

4) Foot deformity

- The anatomy of the foot must be considered in risk calculation. A person with flatfoot is more likely to have disproportionate stress across the foot and may have an increased risk for tissue inflammation in high-stress regions.

PATHOPHYSIOLOGY

Atherosclerosis and peripheral neuropathy occur with increased frequency in persons with diabetes mellitus (DM).

Regarding atherosclerosis, people with diabetes mellitus (DM) have a higher incidence of the disease, thickening of capillary basement membranes, arteriolar hyalinosis, and endothelial proliferation.

The reason for the prevalence of this form of arterial disease in diabetic persons is thought to result from a number of metabolic abnormalities, including high low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL) levels, elevated plasma von Willebrand factor, inhibition of prostacyclin synthesis, elevated plasma fibrinogen levels, and increased platelet adhesiveness.

The pathophysiology of diabetic peripheral neuropathy is multifactorial, the result of loss of sensation in the foot is repetitive stress; unnoticed injuries and fractures; structural foot deformity, such as hammertoes, bunions, metatarsal deformities, or Charcot foot; further stress; and eventual tissue breakdown.

Unnoticed excessive heat or cold, pressure from a poorly fitting shoe, or damage from a blunt or sharp object inadvertently left in the shoe may cause blistering and ulceration. These factors, combined with poor arterial inflow, confer a high risk of limb loss on the patient with diabetes.

CLINICAL FEATURES

Signs and Symptoms:
Patients usually present with symptoms indicative of possible peripheral neuropathy or peripheral arterial insufficiency.

Symptoms of peripheral neuropathy

- Hypoesthesia
- Hyperesthesia
- Paresthesia

- Dysesthesia
- Radicular pain
- Anhydrosis

Symptoms of peripheral arterial insufficiency
Most people harboring atherosclerotic disease of the lower extremities are asymptomatic; others develop ischemic symptoms.

Patients who are symptomatic may present with intermittent claudication, ischemic pain at rest, nonhealing ulceration of the foot, or frank ischemia of the foot.

On physical examination, diabetic ulcers tend to occur in the following areas:

- Areas most subjected to weight bearing, such as the heel, plantar metatarsal head areas, the tips of the most prominent toes (usually the first or second), and the tips of hammer toes (ulcers also occur over the malleoli because these areas commonly are subjected to trauma)
- Areas most subjected to stress, such as the dorsal portion of hammer toes

Other physical findings include the following:

- Hypertrophic calluses
- Brittle nails
- Hammer toes
- Fissures

  There might be signs of possible peripheral arterial insufficiency especially absent or diminished peripheral pulses below a certain level.
  PE might also disclose signs of peripheral neuropathy include:

- Loss of vibratory and position sense
- Loss of deep tendon reflexes (especially loss of the ankle jerk)
- Trophic ulceration
- Foot drop
- Muscle atrophy
- Excessive callous formation, especially overlying pressure points such as the heel.

DIAGNOSIS

- Hx and PE
- Blood tests
  -CBC ; watch for anemia which might impair healing, leukocytosis might be a sign for underlying infection or plantar abcess,
  -Serum glucose, glycohemoglobin, and creatinine levels helps to determine the adequacy of acute and chronic glycemic control and the status of renal function.
  -Blood testing should also include hemoglobin A1c (HbA1c) assessment because a normal value is a surrogate marker for wound healing

- Pulse-volume recording
- Ultrasonography
  -Doppler U/S can help estimate extent of disease and degree of stenosis

- Ankle-brachial index
  - Equals the systolic pressure in the dorsalis pedis or posterior tibial artery divided by the upper extremity systolic pressure
  -Normal = 1.0 , if < 0.9 it suggests atherosclerosis, an ABI below 0.3 suggests a poor chance for healing of distal ischemic ulcerations.
  - The ABI often is falsely elevated (and thus may be unreliable) if the underlying arteries are heavily calcified, a finding common in diabetic persons.

- Radiography
- Computed tomography and MRI (indicated if a plantar abscess is suspected but not clear on physical examination)
- Angiography.

TREATMENT

- Optimal control of blood glucose, and evaluation and correction of peripheral arterial insufficiency.
- Offloading the wound by using appropriate therapeutic footwear
- Daily saline or similar dressings to provide a moist wound environment
- Debridement when necessary
- Antibiotic therapy if osteomyelitis or cellulitis is present

Physicians of diabetic patients with ulcers must decide between the sometimes conflicting options of
(1) performing invasive procedures (eg, angiography, bypass surgery) for limb salvage
(2) avoiding the risks of unnecessarily aggressive management in these patients, who may have significant cardiac risk.

In general, the greatest legal risks are associated with delay in diagnosis of ischemia associated with diabetic ulceration, failure to aggressively debride and treat infection, and failure to treat the wound carefully.

HISTORY & PHYSICAL

Check surgery (OSCE) dossier.

Adrenal Gland

❖ Anatomy:

- Two endocrine glands that produce steroid hormones (from the cortex) and Adrenaline (from the medulla).
- Size: height and thickness are about 5 cm; width is 1–2 cm
- Location:
  - Primary retroperitoneal organs.
  - Each gland is located superior to the upper pole of the kidney.
  - Enclosed by the renal fascia and adipose capsule of the kidney.

❖ Embryology:

- Adrenal cortex: derived from mesoderm
- Adrenal medulla: derived from the neural crest.

❖ Vasculature:

- **Arterial blood supply**
  - Superior suprarenal artery (from the inferior phrenic artery)
  - Medial suprarenal artery (from the abdominal aorta)
  - Inferior suprarenal artery (from the renal artery)
- **Venous drainage**
  - Right suprarenal vein into the inferior cava vein
  - Left suprarenal vein into the left renal vein
- **Lymph drainage:** left aortic lymph nodes; right caval lymph nodes.

❖ Innervation:

- Sympathetic: major and minor splanchnic nerves
- Parasympathetic: vagal nerve

❖ Microscopic anatomy:

Adrenal cortex:

- Surrounded by a fibrous capsule
- Layers of the cortex:
  - **Zona glomerulosa:** cells arranged in oval clusters surrounded by connective tissue from the fibrous capsule.
    Function: mineralocorticoi
    d synthesis.
  - **Zona fasciculata**: cells arranged in straight columns that are separated by small fibrous septa.
    Function:
    glucocorticoid synthesis.
  - **Zona reticularis**: small cells arranged in an irregular netlike formation surrounded by connective tissue and capillaries.
    Function: androgen synthe
    sis.

Adrenal Medulla:

- Large chromaffin cells with many secretory granules (catecholamine Storage)
  - Chromaffin cells originate in the neural crest and migrate to the paraganglia and adrenal medulla during embryonic development.
  - Tumors originating from chromaffin cells are called pheochromocytomas.
- Function: synthesis of catecholamines.

❖ Physiology:

o **CRH** is secreted from the hypothalamus in response to stress, decreased serum cortisol, and in a circadian rhythm. It increases **ACTH** secretion from the anterior pituitary.

o **ACTH** follows a circadian rhythm, **level is highest in the morning.**

o ACTH increases the secretion of all **cortex** hormones, but it has no effect on the adrenal medulla.

Gland & region/ cells	Hormones	Regulation of secretion	Functions
Adrenal cortex Zona glomerulosa	Mineralcorticoids, e.g. aldosterone	Stimulated by angiotensin II	Regulates salt & water balance in blood by increasing Na^+ & H_2O absorption and K^+ secretion by the distal convoluted tubules in the kidney
Adrenal cortex Zona fasciculata	Glucocorticoids, e.g. cortisol & weak androgens	Stimulated by adrenal corticotrophic hormone	Suppresses immune response and regulates carbohydrate metabolism
Adrenal cortex Zona reticularis	Weak androgens, e.g. dehydroepiandrosterone	Stimulated by adrenal corticotrophic hormone	Precursor for testosterone production
Adrenal medulla Chromaffin cells	Catecholamines, e.g. Epinephrine & norepinephrine	Preganglionic sympathetic neurons	Increases heart rate, respiration, and blood pressure Constricts vessels to reduce blood flow to GI tract

Important diseases associated with the:

-> Adrenal cortex:

Hypocortisolism

Hypercortisolism

Primary hyperaldosteronism (Conn syndrome)

Congenital adrenal hyperplasia (CAH)

Androgen-secreting tumors

Important diseases associated with the:

-> Adrenal medulla:

Pheochromocytoma

Neuroblastoma

Cushing's syndrome

INTRODUCTION

Cushing's syndrome, or hypercortisolism, is an endocrine disorder that is most often caused **iatrogenically** by the exogenous administration of glucocorticoids. Less commonly, Cushing's syndrome can result from **endogenous** overproduction of cortisol.

- **Primary hypercortisolism** is the result of autonomous overproduction of cortisol by the adrenal gland (e.g., adrenal adenoma, adrenal carcinoma).
- **Secondary hypercortisolism**, on the other hand, is the result of increased production of adrenocorticotropic hormone (ACTH), either by pituitary microadenomas (Cushing's disease) or by ectopic, paraneoplastic foci (e.g., small cell lung cancer).

ETIOLOGY

It can be either:

1- Exogenous: prolonged glucocorticosteroid therapy, most common cause.
2- Endogenous:

Types	**Primary** (ACTH-independent Cushing syndrome)	**Secondary** (ACTH-dependent)	
		Pituitary ACTH production (**Cushing's disease**)	Ectopic ACTH production
Frequency	5-10%	75%	15%
Sex	Females>Males 4:1	Females>Males 4:1	Females=Males
Causes	Adrenal adenoma Adrenal carcinoma Macronodular adrenal hyperplasia	ACTH secreting pituitary adenoma	Paraneoplastic syndrome (Small cell lung carcinoma, Renal cell carcinoma...)

CLINICAL FEATURES

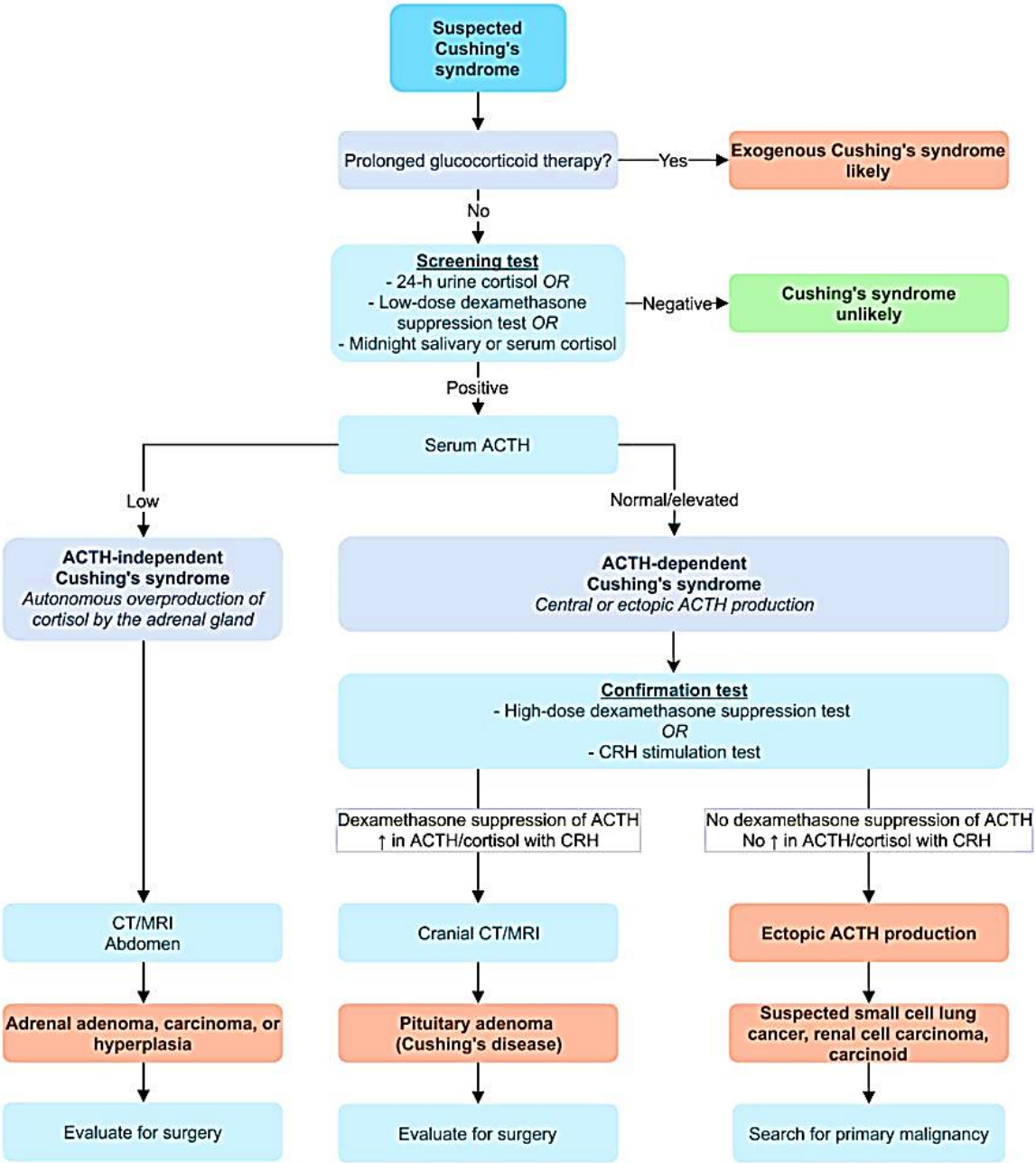
- Skin
  - Thin, easily bruisable skin with stretch marks (classically purple abdominal striae) and/or ecchymoses.
  - Delayed wound healing
  - Flushing of the face
  - Hirsutism
  - Acne
  - If secondary hypercortisolism: often hyperpigmentation, especially in areas that are not normally exposed to the sun (e.g., palm creases, oral cavity)
    - Caused by excessive ACTH production because melanocyte stimulating hormone is cleaved from the same precursor as ACTH.
    - Hyperpigmentation is **not** a feature of primary hypercortisolism.
- Neuropsychological: lethargy, depression, sleep disturbance, psychosis, emotional liability.
- Musculoskeletal
  - Osteopenia, osteoporosis, pathological fractures, avascular necrosis of the femoral head.
  - Muscle atrophy/weakness
- Endocrine and metabolic
  - Insulin resistance → hyperglycemia → mild polyuria in the case of severe hyperglycemia
  - Dyslipidemia

    Weight gain characterized by central obesity, moon faces, and a buffalo hump.
  - ♂: decreased libido
  - ♀: decreased libido, virilization, and/or irregular menstrual cycles
- Secondary hypertension (~ 90% of cases)
- Increased susceptibility to infections
- Peptic ulcer disease
- Cataracts

Note:
Pseudo-Cushing's syndrome is a clinical syndrome that resembles Cushing's in its presentation; however, the adrenals are normal. The most common causes include obesity, alcoholism, and depression.

DIAGNOSIS

1- History and physical would show the clinical features mentioned before.
2- General lab findings: Hyperglycemia, Hypernatremia, Hypokalemia, Hyperlipidemia, Metabolic alkalosis.
3- Tests for hypercortisolism:
   a. ↑ 24-hour urine cortisol
   b. ↑ Early morning serum cortisol levels following a low-dose dexamethasone suppression test.
   c. ↑ Midnight salivary cortisol.



TREATMENT

Exogenous Cushing's syndrome

- Consider lowering the dose of glucocorticoids
- Consider the use of alternatives to glucocorticoids (e.g., azathioprine)

Endogenous Cushing's syndrome

- Operable disease: surgical therapy is the treatment of choice
  - Adrenocortical tumor: laparoscopic or open adrenalectomy
  - Pituitary adenoma: transsphenoidal resection of the pituitary adenoma
  - ACTH-secreting ectopic tumor: resection of the ectopic foci (e.g., bronchial carcinoid)
- Inoperable disease
  - Drugs to suppress cortisol synthesis: metyrapone, mitotane, Ketoconazole.

Pheochromocytoma

INTRODUCTION

Definition: A pheochromocytoma is a catecholamine-secreting tumor typically located in the adrenal medulla.

Epidemiology:

*Age range: 3rd–5th decades of life

*Present in up to 1% of all hypertensive patients

ETIOLOGY

- Tumor arise from **chromaffin cells**, which are derived from the **neural crest**, Locations include:
  - **~ 90% adrenal medulla (physiologically activated by acetylcholine)**
  - ~ 10% extra-adrenal in the sympathetic ganglia
  - ~ 10% at multiple locations
  - The majority of pheochromocytomas are benign, unilateral, catecholamine-producing tumors.
  - Rarely, pheochromocytomas also produce other hormones such as EPO.
- 25% of pheochromocytomas are **hereditary**. Associations include:
  - **Multiple endocrine neoplasia type 2 (MEN 2A, MEN 2B)**
  - **Neurofibromatosis type 1 (NF1)**
  - **Von Hippel-Lindau (VHL) disease**

*"10 percent rule"- roughly 10% of pheochromocytomas are: extra-adrenal, multiple, bilateral, malignant, pediatric cases, not associated with hypertension, show calcifications on imaging!

CLINICAL FEATURES

Clinical presentation is related to fluctuating levels of excess epinephrine, norepinephrine, and dopamine.

- Episodic hypertension (or persistent hypertension in some cases)
- Paroxysmal:
  - Throbbing headache
  - Diaphoresis
  - Heart palpitations and tachycardia
  - Pallor
  - Abdominal pain and nausea
  - Anxiety
- Weight loss due to increased basal metabolism
- Hyperglycemia
- If EPO is secreted, signs of polycythemia
- Other signs and symptoms consistent with associated familial disorders:

  MEN 2A: medullary thyroid cancer, pheochromocytoma, and parathyroid hyperplasia.

  MEN 2B: medullary thyroid cancer, pheochromocytoma, oral/intestinal neuromas, and marfanoid habitus

  NF1: cutaneous neurofibromas, café-au-lait spots, and Lisch nodules

  VHL: renal cell carcinoma, hemangioblastoma, angiomatosis, and pheochromocytoma.

Differential diagnosis:
- Labile essential hypertension
- Anxiety
- Hyperthyroidism
- Hypoglycemia
- Menopausal flushing
- Carcinoid (rare)

DIAGNOSIS

Whenever possible, all medications should be put on hold one week prior to testing.

Best initial test: metanephrines in plasma (high sensitivity)

Confirmatory test: metanephrines and catecholamines in 24-hour urine (high specificity)

Genetic testing: if MEN2A, MEN2B, NF1, or VHL is suspected

Other tests:

- 24-hour ambulatory blood pressure monitoring

- Adrenal/abdominal CT or MRI (after positive biochemistry tests to localize tumor) and other imaging tests to if MEN (2A, 2B) is suspected.

TREATMENT

→ **Operable disease**: Management consists of preoperative blood pressure management and then surgery.

- Preoperative blood pressure management: Combined alpha and beta-adrenergic blockade
  - **First**, a **non-selective alpha blocker** is given: **phenoxybenzamine** blocks alpha-1 and alpha-2 adrenoceptors equally and irreversibly.
  - **After** sufficient alpha-adrenergic blockade, a **beta blocker** may be started for additional blood pressure control and control of tachyarrhythmias.
- Treatment of choice: laparoscopic tumor resection (adrenalectomy)
  - "No-touch" technique (squeezing the mass might release massive amount of catecholamines).
  - Open surgical resection is reserved for large or invasive tumors.

Important: Starting beta blockers before alpha blockade is contraindicated. Beta blockers cancel out the vasodilatory effect of peripheral beta-2 adrenoceptors, potentially leading to:

Unopposed alpha-adrenoceptor stimulation → vasoconstriction → **hypertensive crisis**

→ **Inoperable disease**

- **Benign pheochromocytoma:** primary therapy with phenoxybenzamine.
- **Malignant pheochromocytoma:** MIBG therapy; otherwise, palliative treatment (chemotherapy, tumor embolization).

Adrenal Incidentaloma

An **adrenal incidentaloma** is a mass lesion **greater than 1 cm** in diameter, discovered by radiologic examination (CT or MRI). Most of them are non-functioning masses and up to 15% are bilateral masses.

➔ All patients with incidentalomas should have the following tests:

⚜ **Blood pressure and serum potassium** (Zona glomerulosa)

◎ **Low DST and 24-hour urine cortisol** (Zona fasciculata)

◎ **Plasma fractionated metanephrine** (to exclude pheochromocytoma)

◎ Females with **virilization** or males with **feminization** should have their **Androgens** tested.

*If results are normal and mass <4 cm; observe and repeat image in 3-6 Months.

➔ The mass can be:

• **Benign cortical adenoma:** A homogeneous adrenal mass <4 cm in diameter, with a smooth border, and an attenuation value <10 Hounsfield unit (HU) on unenhanced CT, and rapid contrast medium washout (>50 percent at 10 minutes).

• **Adrenal carcinoma or metastases:** irregular shape, inhomogeneous density, high unenhanced CT attenuation values (>20 HU), delayed contrast medium washout (<50 percent at 10 minutes), diameter usually >4 cm, and tumor calcification.

• **Pheochromocytoma** should be excluded in all patients by measuring 24-hour urinary fractionated metanephrines and catecholamines.

• **Subclinical Cushing's syndrome** should be ruled out by performing the 1 mg overnight dexamethasone suppression test (DST). If the test is abnormal, confirm with 24H urine cortisol.

• **Aldosteronomas:** If the adrenal incidentaloma patient is hypertensive, a plasma aldosterone-to-plasma renin activity ratio and plasma potassium concentration should be obtained to screen for primary aldosteronism.

Multiple Endocrine Neoplasia (MEN)

INTRODUCTION

Multiple endocrine neoplasia **(MEN)** is a term used to describe three **autosomal dominant syndromes** that are associated with certain hormone-producing neoplasias. There are three subtypes: **MEN 1**, **MEN 2A** and **MEN 2B**.

MEN 1 is caused by an altered **menin** protein expression and presents with primary **hyperparathyroidism**, often in association with endocrine **pancreatic tumors and/or pituitary adenomas**.

MEN 2A and MEN 2B are caused by a mutated **RET** proto-oncogene and both present with **medullary thyroid carcinoma** and sometimes **pheochromocytoma**.

MEN 2A is further associated with primary **hyperparathyroidism** as well, while **MEN 2B** causes **a Marfanoid habitus** and sometimes **neurinomas**.

If any of the individual conditions associated with MEN are suspected, especially in patients with a **positive family history**, it is important to consider a diagnostic workup for any of the other associations.

Those positive for mutated genes should be closely monitored and should undergo **a total thyroidectomy if positive for the RET proto-oncogene**. At the age of:

5 years if **MEN 2A**

1 year if **MEN 2B** (more aggressive presentation).

	MEN 1 Wermer's syndrome	MEN2	
		MEN 2A Sipple's syndrome	MEN 2B
Genetics	Altered menin protein expression	Altered expression of the RET proto-oncogene → elevated tyrosine kinase activity	
Main disease	Primary hyperparathyroidism (~ %90 of cases)	Medullary Thyroid Cancer (almost %100 of cases)	
Other manifestations	• Endocrine pancreatic tumors (~ 50–80% of cases) such as gastrinoma (most common) and insulinoma • Pituitary adenoma (~ 30–50% of cases): most commonly prolactinoma • Carcinoid tumors (~ 10–15% of cases)	Pheochromocytoma (around %40 of cases)	
		Primary hyperparathyroidism (%20-%30)	*Multiple neurinomas *Marfanoid habitus (more than %95)
Management	• Parathyroidectomy • Excision of pancreatic tumor. • Transsphenoidal surgery for pituitary adenoma.	• Thyroidectomy including cervical lymph nodes ○ Pheochromocytoma should first be ruled out or treated before undergoing surgery • If pheochromocytoma (adrenalectomy) • If hyperparathyroidism: remove pathologic parathyroid glands (parathyroidectomy)	
Remember	**3Ps** ***Parathyroid** ***Pancreas** ***Pituitary**	**1M 2Ps** ***Medullary thyroid CA** ***Pheochromocytoma** ***Parathyroid**	**2Ms 1P** ***Marfanoid habitus** ***Multiple neurinomas** ***Pheochromocytoma**

References:

1- UpToDate.
2- Amboss.
3- Medscape.
4- Surgical recall.
5- Old dossier.

The End

Good Luck