

ENDOCRINE

**HIGH YIELD
NOTES**

**BY
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PATHOLOGY

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NOTES

ADRENAL HYPERFUNCTION

GENERALLY, WHAT IS IT?

PATHOLOGY & CAUSES

- Overproduction of \geq one adrenal hormones
→ complex systemic disorders

CAUSES

- Pituitary/adrenal endocrine tumors
- Idiopathic, iatrogenic
- Increased aldosterone → hyperaldosteronism
- Increased cortisol → Cushing syndrome

SIGNS & SYMPTOMS

- Diffuse systemic symptoms due to systemic endocrine effects

DIAGNOSIS

DIAGNOSTIC IMAGING

CT scan/MRI

- Image tumors

LAB RESULTS

- Blood/urine tests; measure hormone levels

TREATMENT

- See individual disorders

CONN'S SYNDROME

osms.it/conns-syndrome

PATHOLOGY & CAUSES

- Type of primary hyperaldosteronism

CAUSES

- Adrenal glands produce too much aldosterone due to benign tumor (adrenal adenoma)
 - Forms in zona glomerulosa in adrenal gland

RISK FACTORS

- Individuals who are biologically female, 20–60 years old, with family history

SIGNS & SYMPTOMS

- Headache, facial flushing (due to hypertension)
- Constipation, muscle weakness, arrhythmias (if severe, due to hypokalemia)
 - Low potassium, high blood pressure (BP); unresponsive to treatment

DIAGNOSIS

DIAGNOSTIC IMAGING

CT scan

- Abdominal CT scan to differentiate tumor from idiopathic hyperaldosteronism

LAB RESULTS

- Adrenal vein sampling (CT scans do not detect lesions < 1cm/0.39in)

TREATMENT

SURGERY

- Unilateral adrenalectomy

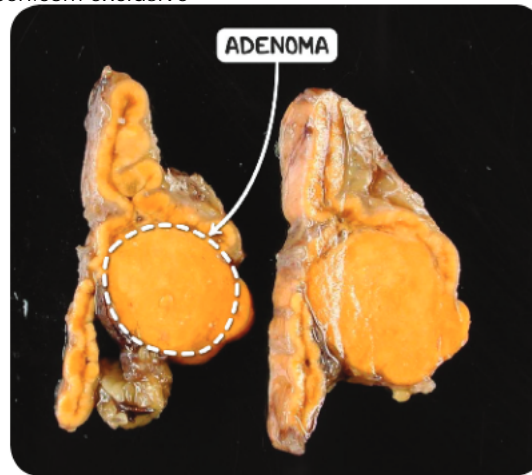


Figure 11.1 The gross pathological appearance of an adrenal cortical adenoma in an individual with Conn's syndrome.

CUSHING'S SYNDROME

osms.it/cushings-syndrome

PATHOLOGY & CAUSES

- Endocrine disorder caused by increased cortisol
- Can be endogenous (caused by cortisol production inside body)/exogenous (iatrogenic)
- *Pseudo Cushing's syndrome*: estrogen-containing oral contraceptive pills → increased cortisol-binding globulin → increased total cortisol
 - Active hormone total free cortisol levels found in a 24-hour urine sample normal

CAUSES

Primary

- Tumor in zona fasciculata of adrenal gland secretes cortisol
- Adenoma (benign)/adenocarcinoma (malignant)

Secondary

- Iatrogenic

- Glucocorticoid steroid medications to treat inflammatory, autoimmune disorders (e.g. asthma, rheumatoid arthritis, eczema, immunosuppression); most common
- Pituitary adenoma (benign)
 - Leads to excess adrenocorticotrophic hormone (ACTH), adrenal cortisol secretion
- Adrenal Cushing's disease
 - Adrenal gland tumors/hyperplastic adrenal glands/nodular adrenal hyperplasia of adrenal glands produce excess cortisol
- Ectopic ACTH
 - Increased ACTH secreted from benign bronchial carcinoid tumors/malignant oat-cell carcinoma

COMPLICATIONS

- Metabolic syndrome, diabetes, infection due to immunosuppression, fragility fractures due to osteoporosis

SIGNS & SYMPTOMS

- Fat redistribution due to glucose release → insulin release
- Muscle, bone, skin breakdown due to protein breakdown
- Hypertension due to corticosteroids cross-reacting with mineralocorticoid receptors
- High cortisol → feedback inhibition of GH-releasing hormone (GRH) → disrupts ovarian, testicular function



Figure 11.2 Abdominal striae in an individual with Cushing's syndrome.



MNEMONIC: BAM CUSHINGOID

Signs & symptoms of Cushing's syndrome

Buffalo hump: fat redistribution

Amenorrhea

Moon face: fat redistribution

Psycho^sis/agitation: previously,
Crazed

Ulcers

Skin changes: acne, purple
striae/stretch marks

Hypertension

Infection: due to
immunosuppression

Necrosis of femoral head

Glaucoma

Osteoporosis: causing fragility
fractures

Immunosuppression

Diabetes

DIAGNOSIS

DIAGNOSTIC IMAGING

CT scan

- Adrenal glands (primary Cushing's)
- Chest, abdomen, pelvis (ectopic ACTH production)

MRI

- Pituitary gland (Cushing's disease)

LAB RESULTS

- ↑ free cortisol in 24-hour urine sample
- *Cortisol blood/saliva test*: ↑ cortisol
 - Performed in evening when cortisol levels are normally low

OTHER DIAGNOSTICS

Dexamethasone suppression test

- Differentiates endogenous, exogenous Cushing's syndrome
- Measure cortisol change after dexamethasone (exogenous steroid)
- *Endogenous Cushing's syndrome*: cortisol unchanged, negative feedback cycle broken by autonomous endocrine tumor in pituitary, adrenal, etc. (ectopic ACTH)
- Positive dexamethasone test
 - *High ACTH*: ACTH-producing tumor
 - *Low ACTH*: adrenal tumor, causing pituitary ACTH suppression

Long dexamethasone suppression test

- If high ACTH
- Differentiates ACTH-producing pituitary tumor, ectopic ACTH-producing tumor (e.g. small cell lung cancer)
 - *Cushing's disease (pituitary adenoma)*: cells partly responsive to negative feedback → cortisol decrease
 - *Ectopic ACTH-producing tumor*: no negative feedback → cortisol unchanged

TREATMENT

MEDICATIONS

- Cortisol inhibitors
 - Esp. if surgery ruled out by ectopic ACTH production/metastatic adrenal carcinoma
- Wean steroid medications
 - For iatrogenic Cushing's
 - Sudden withdrawal → adrenal crisis

SURGERY

- Transphenoidal resection of pituitary gland
 - For Cushing disease
- Surgical resection
 - For adrenal adenoma



Figure 11.3 A large fat deposit at the upper back in an individual with Cushing's syndrome.

HYPERALDOSTERONISM

osms.it/hyperaldosteronism

PATHOLOGY & CAUSES

- Adrenal gland produces **excess aldosterone** → hypertension (high blood pressure), hypokalemia (decreased blood potassium)
- Increased aldosterone → sodium, water retention → increased blood volume → hypertension

TYPES

Primary

- **Idiopathic** ($2/3$ of cases): overproduction from both adrenal glands
- **Conn's syndrome** ($1/3$ of cases): benign adrenal tumor → excess aldosterone
- **Familial hyperaldosteronism**: rare genetic condition, adrenocorticotrophic hormone (ACTH) → adrenal aldosterone, renin secretion

Secondary

- Hypotension (e.g. congestive heart failure, cor pulmonale, hypoalbuminemia, cirrhosis, ascites, coarctation of aorta) → renin-

angiotensin-aldosterone axis activation → hyperaldosteronism

- Decreased blood flow to kidneys (e.g. renal stenosis)
- Renal-secreting neoplasms

COMPLICATIONS

- Hypertension, hypokalemia
 - Heart disease (ischemic heart disease, arrhythmias), vascular disease, renal disease, stroke, alkalosis (due to increased hydrogen ion excretion)

SIGNS & SYMPTOMS

- Headache, facial flushing (due to hypertension)
- Constipation, muscle weakness, arrhythmias (if severe, due to hypokalemia)

DIAGNOSIS

LAB RESULTS

- Renin, aldosterone levels in blood and urine
- Primary
 - Increased aldosterone, decreased renin; potassium decreased/normal
 - Metabolic acidosis secondary to hypokalemia
- Secondary
 - Increased renin, aldosterone in blood

OTHER DIAGNOSTICS

- Increased blood pressure

TREATMENT

- Goal: prevent complications of hyperaldosteronism on organs (e.g. ventricular hypertrophy, heart failure, stroke, myocardial infarction, atrial fibrillation, metabolic syndrome)

MEDICATIONS

- Potassium-sparing diuretic/aldosterone antagonist
 - Spironolactone
- Additionally
 - Thiazide diuretics, angiotensin converting enzyme inhibitors (ACE) inhibitors, calcium channel antagonists, angiotensin II blockers

OTHER INTERVENTIONS

- Control BP via lifestyle
 - Sodium restriction, weight management, regular exercise
- Second-line
 - Thiazide diuretics, ACE inhibitors, calcium channel antagonists, angiotensin II blockers



NOTES

ADRENAL HYPERPLASIA

CONGENITAL ADRENAL HYPERPLASIA

osms.it/congenital-adrenal-hyperplasia

PATHOLOGY & CAUSES

- Congenital adrenal hyperplasia (CAH) is a group of autosomal-recessive metabolic disorders characterized by defects in certain genes resulting in a partial/total lack of an enzyme involved in steroidogenesis within the adrenal cortex
 - ↓ steroid hormone production → compensatory ↑ ACTH → adrenal hyperplasia
 - ↓ cortisol → cortisol precursor accumulation → steroid precursors shunted to overproduction of other ACTH-dependent adrenal steroids

TYPES

21-hydroxylase deficiency

- Defective gene: CYP21A2
- Most common type of CAH
 - **Classic:** neonatal/early infancy genital ambiguity in females, adrenal insufficiency; classic non-salt-losing (simple virilizing): female fetus virilization; classic salt-losing
 - **Non-classic (late onset):** presents later in life (child-adult) with androgen excess signs; non-salt-losing

17-alpha hydroxylase deficiency

- Defective gene: CYP17A1
- Rare
- Steroid precursors for testosterone, cortisol synthesis shunted to aldosterone

11-beta-hydroxylase deficiency

- Defective gene: CYP11B1
- 7% of CAH cases
- Lack of enzyme prevents conversion of 11-deoxycortisol to cortisol
- 11-deoxycortisol (aldosterone precursor) has mild mineralocorticoid effect → biphasic effect on mineralocorticoid balance

SIGNS & SYMPTOMS

21-hydroxylase deficiency

- Varies by subtype

17-alpha hydroxylase deficiency

- ↓ cortisol → corticosterone presence prevents adrenal crisis
- Mineralocorticoid excess → secondary hypertension; hypokalemic alkalosis
- Gonadocorticoid deficiency (males: mildly underdeveloped genitalia, hypergonadotropic hypogonadism; females: abnormal pubertal sexual development, infertility)

11-beta-hydroxylase deficiency

- Androgen excess → external genitalia virilization, sexual ambiguity (females)
- Biphasic mineralocorticoid balance → possible salt-wasting crisis in early infancy; secondary hypertension and hypokalemia in childhood and adult life



Figure 12.1 Clitoromegaly with normal labia and introitus in a biologically female individual with 21-hydroxylase deficiency.

DIAGNOSIS

- Clinical presentation
 - Steroid imbalance evidence
- Most cases identified via newborn screening

LAB RESULTS

Serum hormone levels

- 21-hydroxylase deficiency
 - ↓ sodium (salt-losing type), ↑ potassium (salt-losing type)
 - **Serum markers:** ↑↑ serum 17-hydroxyprogesterone, ↑ 21-deoxycortisol
- 17-alpha hydroxylase deficiency
 - ↑ sodium, ↓ potassium
 - **Serum markers:** ↑ pregnenolone, ↑ progesterone, ↑ 11-deoxycorticosterone, ↑ 11-deoxycortisol
- 11-beta-hydroxylase deficiency
 - ↑ sodium, ↓ potassium
 - **Serum markers:** ↑ 11-deoxycorticosterone, ↑ 11-deoxycortisol

Genetic testing

Prenatal diagnosis

- By chorionic villus sampling at 10–12 weeks

TREATMENT

MEDICATIONS

- 21-hydroxylase deficiency
 - Exogenous glucocorticoid (hydrocortisone), mineralocorticoid (fludrocortisone)
- 11-beta-hydroxylase deficiency
 - Exogenous glucocorticoid (hydrocortisone), antihypertensives
- 17-alpha hydroxylase deficiency
 - Exogenous glucocorticoid (hydrocortisone), sex steroid replacement beginning at puberty, antihypertensives
- If CAH diagnosed prenatally
 - Dexamethasone

SURGERY

- Potential atypical genitalia correction

OTHER INTERVENTIONS

- Address complications (e.g., fluid, electrolyte imbalance)
- Monitor
 - Serum 17-hydroxyprogesterone, renin, electrolytes
 - Blood pressure
 - Bone age and density
 - Tanner staging
 - Weight
 - Growth velocity

21-HYDROXYLASE DEFICIENCY OVERVIEW

	CLASSIC SALT-LOSING	CLASSIC SIMPLE VIRILIZING	CLASSIC
AGE AT PRESENTATION	- Early neonatal period	- Neonatal - 4 years	- Adult-child (late onset)
EFFECTS ON GENITALIA	<ul style="list-style-type: none"> - Females: ambiguous - Males: normal; may have scrotal hyperpigmentation; enlarged phallus 	<ul style="list-style-type: none"> - Females: ambiguous - Males: normal; early virilization (pubic hair, growth spurt, adult body odor) at 2-4 years of age; testicular adrenal rest tumors may develop between 10-20 years of age 	<ul style="list-style-type: none"> - Females: virilized - Males: normal
HORMONE PRODUCTION	<ul style="list-style-type: none"> - ↓ cortisol - ↓ aldosterone - ↑ androgens 	<ul style="list-style-type: none"> - ↓ cortisol - Normal aldosterone - ↑ androgens 	<ul style="list-style-type: none"> - Normal cortisol, aldosterone - ↑ androgens
OTHER EFFECTS	<ul style="list-style-type: none"> - First 2 weeks of life: may present with hypotension and salt-wasting crisis (poor feeding, vomiting, failure to thrive, lethargy), hypoglycemia, hypotension 	<ul style="list-style-type: none"> - Males: premature pubarche (pubic hair, growth spurt, adult body odor) at 2-4 years of age; testicular adrenal rest tumors may develop between 10-20 years of age - Premature epiphyseal closure → adult height diminished 	<ul style="list-style-type: none"> - Males/females: premature pubarche - Females: hirsutism, menstrual irregularity - ↑ risk of stress-induced adrenal insufficiency



NOTES

ADRENAL HYPOFUNCTION

GENERALLY, WHAT IS IT?

PATHOLOGY & CAUSES

- Disorders of adrenal cortex resulting in loss of essential steroid hormones (corticosteroids, mineralocorticoids, androgens)

CAUSES

- Addison's disease
 - Multiple causes; primarily autoimmune
- Waterhouse–Friderichsen syndrome (WFS)
 - Primarily caused by meningococcal infection, sepsis

COMPLICATIONS

- Adrenal crisis
 - Addison's, WFS
- Disseminated intravascular coagulation
 - WFS

SIGNS & SYMPTOMS

- Hypoglycemia, hypotension, electrolyte imbalance
- Adrenal crisis:** dehydration, electrolyte imbalance, shock

DIAGNOSIS

DIAGNOSTIC IMAGING

Ultrasound, CT scan

- Visualizes enlarged, calcified, solid/hemorrhagic glands

OTHER DIAGNOSTICS

- Rapid adrenocorticotrophic hormone (ACTH) test confirms adrenal hypofunction

TREATMENT

MEDICATIONS

- Hormone replacement:** hydrocortisone, fludrocortisone
 - Dehydroepiandrosterone (DHEA) in some cases

OTHER INTERVENTIONS

- Treat underlying cause

ADDISON'S DISEASE

osms.it/addisons-disease

PATHOLOGY & CAUSES

- Endocrine disorder characterized by **primary adrenal insufficiency** due to bilateral adrenal cortex destruction
- Adrenal cortex destruction → ↓ production of adrenocortical hormones → **glucocorticoid, mineralocorticoid, androgen deficiency**
 - Adrenals only source of androgens in biologically-female individuals; testicles supply androgens in biologically-male individuals
- ↓ **cortisol** → ↓ adrenal medullary epinephrine synthesis → ↓ serum epinephrine, compensatory norepinephrine production

CAUSES

- **Autoimmune destruction** (e.g. polyglandular autoimmune syndrome type 2)
- **Infection** (e.g. tuberculosis, fungal infections)
- Adrenal hemorrhage (e.g. WFS)
- Adrenal vein thrombotic infarction
- Metastatic infiltration
- Drugs that inhibit cortisol biosynthesis (e.g. ketoconazole, suramin)

COMPLICATIONS

- Addisonian crisis precipitated by physiologically stressful events (e.g. surgical procedures, trauma, infection, dehydration)

SIGNS & SYMPTOMS

- Fatigue, weakness are common initial symptoms
- **Hypotension**, postural hypotension, syncope
 - ↓ glucocorticoids → ↓ vascular responsiveness to angiotensin II and

norepinephrine

- **Hyponatremia**
 - Mineralocorticoid deficiency → sodium loss + ↓ volume due to ↑ vasopressin secretion secondary to ↓ cortisol
- **Hyperkalemia**, mild hyperchloremic acidosis due to mineralocorticoid deficiency
- Hypoglycemia due to ↓ gluconeogenesis
- Gastrointestinal
 - Abdominal pain, anorexia, nausea, vomiting → weight loss
- Intolerance of temperature extremes
- **Hyperpigmentation** due to ACTH stimulation of melanocyte activity
- Vitiligo due to autoimmune destruction of melanocytes
- Salt cravings due to hyponatremia
- ↓ libido, ↓ pubic, axillary hair in biologically-female individuals due to ↓ adrenal androgens
- Psychiatric symptoms (e.g. confusion, depression)
- Addisonian crisis triggered by stress
 - Hypoglycemia
 - Vasomotor/circulatory collapse; shock may be unresponsive to vasopressors due to ↓↓ cortisol, potentially fatal



Figure 13.1 An example of increased skin pigmentation in an individual with Addison's disease (left) and resolution post-treatment (right).



Figure 13.2 Hyperpigmentation of the gums in an individual with Addison's disease.

- ↑ serum ACTH
- Plasma renin activity
 - ↑ renin, compensatory to ↓ aldosterone
- ↓ serum sodium, ↑ serum potassium, mild hyperchloremic acidosis

OTHER DIAGNOSTICS

- History, physical examination with characteristic findings
- Rapid ACTH test
 - Administer 250µg synthetic ACTH (cosyntropin) intravenous (IV)/intramuscular (IM) → insufficient/no cortisol produced in response

DIAGNOSIS

DIAGNOSTIC IMAGING

Abdominal CT scan

- Enlarged adrenal glands with tuberculosis/malignant mass; small if autoimmune adrenalitis/advanced tuberculosis; calcifications if infectious cause
- Visualizes adrenal gland hemorrhage/thrombosis

Abdominal X-ray

- Adrenal calcifications if infectious cause

LAB RESULTS

- ↓ serum cortisol
 - Blood draw in AM when cortisol levels should peak

TREATMENT

MEDICATIONS

- Life-long glucocorticoid replacement; e.g. hydrocortisone, mineralocorticoid replacement
 - E.g. fludrocortisone
- Biologically-female individuals may need low dose dehydroepiandrosterone (DHEA)
- Addisonian crisis
 - Glucocorticoids, epinephrine, glucose, isotonic fluids
- Stress dose of glucocorticoid during any surgical intervention/significant trauma
 - Premedication/induction-maintenance-gradual titration to baseline dose

WATERHOUSE–FRIDERICHSEN SYNDROME

osms.it/waterhouse-friderichsen

PATHOLOGY & CAUSES

- Uncommon, severe syndrome characterized by adrenal failure related to overwhelming infection, adrenal gland hemorrhage
- Bacterial infection → septicemia → release of bacterial endotoxins → endothelial dysfunction → seeding of bacterial emboli into adrenals → bleeding into one/both

adrenal glands → hemorrhagic necrosis →
adrenocortical insufficiency → adrenal crisis

CAUSES

- Associated with sepsis caused by organisms (e.g. *Neisseria meningitidis* (80% of cases), *Streptococcus pneumoniae*, *Neisseria gonorrhoeae*, *Escherichia coli*, *Haemophilus influenzae*, *Staphylococcus aureus*)

COMPLICATIONS

- Disseminated intravascular coagulation (DIC)
- Profound shock
- Potentially life-threatening

SIGNS & SYMPTOMS

- **Initial presentation:** malaise, fever, chills, headache, vomiting
- Signs of shock (e.g. hypotension, tachycardia, tachypnea)
- Widespread petechial lesions → purpura → plaques
- Cyanosis, AKA dusky gray color of skin

DIAGNOSIS

DIAGNOSTIC IMAGING

CT scan

- Identifies blood collection within adrenals

Ultrasound

- Adrenal hemorrhage appears solid, diffusely echogenic

LAB RESULTS

- Blood culture
 - Identifies causative organism
- Adrenal insufficiency
 - ↓ serum sodium, ↓ glucose, ↑ potassium, ↓ serum cortisol
- DIC
 - ↑ fibrinogen degradation products, ↑ D-dimer levels, prolonged PT, aPTT

OTHER DIAGNOSTICS

- History, physical examination with characteristic findings
- Rapid ACTH test
 - Insufficient/no cortisol produced indicates adrenal insufficiency

TREATMENT

MEDICATIONS

- Adrenal insufficiency
 - IV glucocorticoids
- Infection
 - Antibiotics (e.g. IV penicillin, cefotaxime/ceftriaxone if meningococcal infection)
- Shock
 - IV fluids, vasopressors, supplemental oxygen
- DIC
 - Packed red blood cells (RBCs), cryoprecipitate, fresh frozen plasma, platelets

OTHER INTERVENTIONS

- Prevention
 - Routine vaccination against meningococcal disease



NOTES

DIABETES MELLITUS

GENERALLY, WHAT IS IT?

PATHOLOGY & CAUSES

- A group of chronic disorders characterized by abnormal glucose metabolism resulting in elevated blood glucose levels

CAUSES

- Genetic predisposition, lifestyle factors

COMPLICATIONS

- Hyper/hypoglycemia, diabetic ketoacidosis, hyperosmolar hyperglycemic state (HHS), vascular and neurological pathology, renal disease

SIGNS & SYMPTOMS

- Symptomatic hyperglycemia

DIAGNOSIS

LAB RESULTS

Urinalysis

- Albuminuria, glycosuria

Blood tests

- ↑ Non-fasting/fasting glucose tests
- ↑ HbA_{1c}
- Diabetic ketoacidosis (DKA)
 - Glucose > 250mg/dL
- Hyperosmolar hyperglycemic state (HHS)
 - Glucose > 600mg/dL

OTHER DIAGNOSTICS

Physical examination

- Fundoscopic exam
 - Cotton wools spots, flare hemorrhages
- Monofilament testing
 - ↓ sensation
- Lower extremities
 - ↓ pedal pulses, presence of ulcers

TREATMENT

MEDICATIONS

- Diabetes mellitus type I
 - Insulin
- Diabetes mellitus type II
 - Oral antidiabetic agents, insulin

OTHER INTERVENTIONS

- Metabolism regulation with diet
- Weight loss, exercise
- Smoking cessation

DIABETES MELLITUS TYPE 1

osms.it/diabetes-mellitus-type-1

PATHOLOGY & CAUSES

- Chronic metabolic disease; destroys pancreatic beta cells → insulin deficiency, hyperglycemia
- Diabetes (going through) mellitus (honey/sweet)
- ↓ insulin → glucose unable to enter cells → hyperglycemia
 - Cells “starve” due to no glucose for energy generation → polyphagia, fatigue
 - Glucose exceeds renal threshold → glycosuria → osmotic diuresis → polyuria → hypovolemia
 - ↑ serum osmolality + hypovolemia → polydipsia
 - Endothelial glycosylation (endothelial cells unable to downregulate glucose transport in setting of extracellular hyperglycemia) → damage to endothelial cells → microvascular damage + accelerated atherosclerosis in large vessels
 - Narrowing of vascular lumens → ↓ microcirculation → tissue ischemia, cellular loss
 - ↓ blood supply to nerves → segmental demyelination → slowing of nerve conduction neuropathy

TYPES

Type 1A: immune-mediated diabetes

- Most common
- Autoimmune destruction of pancreatic beta-cells
- Type IV hypersensitivity response

Type 1B: idiopathic diabetes

- No evidence of autoimmunity
- Varying degrees of low insulin, episodes of ketoacidosis

Latent autoimmune diabetes

- Progressive form of autoimmune diabetes
- Onset at > 30 years old

RISK FACTORS

- Genetic predisposition
- Multiple gene polymorphisms associated with DM Type I
 - HLA-DQalpha, HLA-DQbeta, HLA-DR, PTPN22 gene, CTLA-4

COMPLICATIONS

- ↑ risk of infection, delayed wound healing; ↑ risk of amputations
- Diabetic ketoacidosis
 - Hyperglycemia (> 250mg/dL), ketonemia, metabolic acidosis
- Neuropathy
 - Autonomic, somatic

Microvascular

- Retinopathy, nephropathy, erectile dysfunction

Macrovascular

- Cardiovascular, cerebrovascular, and peripheral vascular disease

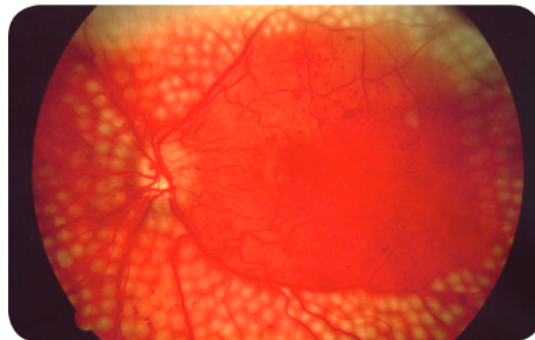


Figure 14.1 A retinal photograph of an individual who has received laser treatment for proliferative retinopathy as a consequence of diabetes mellitus.



Figure 14.2 An individual with diabetes mellitus and charcot arthropathy of the left ankle. Lack of sensation to the joint causes results in repetitive microtrauma which eventually leads to bony destruction and joint malformation.

SIGNS & SYMPTOMS

- **Classic presentation:** polyuria, polydipsia, polyphagia (3Ps)
 - Dehydration → dry mucous membranes/ decreased skin turgor
- Fatigue, lethargy
- Blurred vision
- Gastroparesis → constipation
- Paresthesias
- Unexplained weight loss
- **Mild hyperglycemia**, may be asymptomatic
- **Volume depletion:** symptomatic moderate to severe hyperglycemia
 - Dry mucous membranes, hypotension, poor skin turgor

DIAGNOSIS

LAB RESULTS

Non-fasting/random glucose test

- 200mg/dL

Fasting glucose test

- Prediabetes: 110–125mg/dL
- Diabetes: ≥ 126 mg/dL

HbA1c glycated hemoglobin test

- Indicates glucose level control over prolonged period
- Prediabetes: 5.7–6.4% HbA1c
- Diabetes: $> 6.5\%$ HbA1c

Urinalysis

- Albuminuria, glycosuria

Differentiation from Type II diabetes

- **Autoantibodies against beta cells:** glutamic acid decarboxylase autoantibodies (GADA), insulinoma-associated-2 autoantibodies (IA-2A), islet cell autoantibodies, insulin autoantibodies (IAA), zinc transporter 8 (ZnT8Ab)
- C-peptide: insulin low

OTHER DIAGNOSTICS

Physical examination

- **Fundoscopy exam:** cotton wools spots, flare hemorrhages
- **Monofilament testing:** ↓ sensation
- **Lower extremities:** ↓ pedal pulses, presence of ulcers



Figure 14.3 A neuropathic ulcer on the heel of an individual with diabetes mellitus.

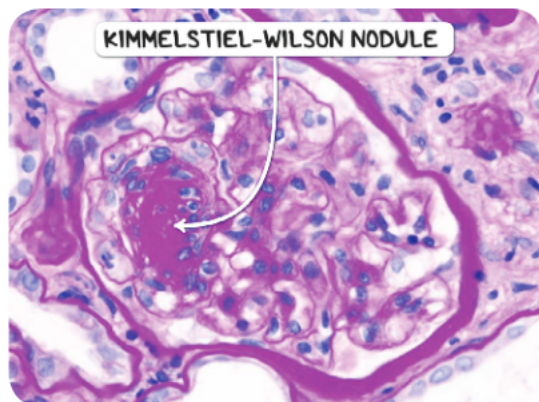


Figure 14.4 The histological appearance of a glomerulus in an individual with diabetes mellitus. The glomerular basement membrane is thickened and there is mesangial proliferation leading to the appearance of a Kimmelstiel–Wilson nodule.

TREATMENT

MEDICATIONS

- Lifelong **insulin** therapy (short-acting insulin/insulin pump)

DIABETES MELLITUS TYPE II

osms.it/diabetes-mellitus-type-2

PATHOLOGY & CAUSES

- Metabolic disorder; varying degrees of resistance to insulin
- Most common type of diabetes in adults (90–95%)

CAUSES

- Insulin resistance (inherited, acquired) → beta cell hyperplasia, hypertrophy → ↑ beta cell secretion of insulin + amylin production → hyperinsulinemia, amyloid deposits within beta cells → beta cell exhaustion, dysfunction, atrophy → ↓ insulin production → hyperglycemia
- Genetic polymorphisms associated with DM Type II
 - TCF7L2, GCK, HNF1B, WFS1, KCNJ11, PPARG, IRS1

RISK FACTORS

- Multifactorial; interaction between genetic, environmental, behavioral factors

- Family history, physical inactivity, poor diet, obesity, > 45 years old, history of gestational diabetes, prediabetes, polycystic ovary syndrome (PCOS), medications that adversely affect glucose tolerance/↑ blood glucose levels (e.g. glucocorticoids, atypical antipsychotics, thiazide diuretics)

COMPLICATIONS

- ↑ risk of **cardiovascular**, peripheral artery disease

Hyperosmolar hyperglycemic state (HHS)

- Profound hyperglycemia (>600mg/dL) → ↑ plasma osmolarity (>320mOsm/kg) → systemic, cellular dehydration
- Mental status changes; thrombotic events; polyuria; mild ketonemia, acidosis; high mortality rate

SIGNS & SYMPTOMS

- Polyuria, polydipsia, polyphagia; glycosuria, weakness, unexplained weight loss, blurred vision; acanthosis nigricans (hyperpigmented cutaneous patches) related to insulin resistance

DIAGNOSIS

LAB RESULTS

Non-fasting/random glucose test

- 200mg/dl

Fasting glucose test

- Prediabetes: 110–125mg/dl
- Diabetes: 126mg/dl

Oral glucose tolerance test

- Prediabetes: 99–140mg/dl
- Diabetes: ≥ 200

HbA_{1c} glycated hemoglobin

- Prediabetes: 5.7–6.4%
- Diabetes: $> 6.5\%$

Differentiation from Type I

- Autoantibodies
 - Absent
- C peptide
 - Normal/elevated

OTHER DIAGNOSTICS

Physical examination

- Fundoscopic exam: cotton wool spots, flare hemorrhages
- Monofilament testing: ↓ sensation
- Lower extremities: ↓ pedal pulses, presence of ulcers

TREATMENT

MEDICATIONS

- Metformin; sulfonylureas, meglitinides
- Long/short-acting insulin

OTHER INTERVENTIONS

- Weight loss, exercise, diet management

DIABETIC KETOACIDOSIS

osms.it/diabetic-ketoacidosis

PATHOLOGY & CAUSES

- Medical emergency due to cell starvation → altered mental status
- Arises with stress/infection, individuals with poorly regulated glucose levels
- Epinephrine → glucagon → lipolysis → free fatty acids → ketone bodies, acetoacetic, hydroxybutyric acid → ↑ blood acidity
- Occurs in Type I, long-standing Type II DM when body completely stops producing insulin

COMPLICATIONS

- Acute cerebral edema
 - High glucose → osmotic shift of water to extracellular fluid
- Hyperkalemia due to H⁺/K⁺ exchange mechanisms in regulating acidosis → arrhythmias

RISK FACTORS

- Infection, stress, irregular insulin use

SIGNS & SYMPTOMS

- Anion gap metabolic acidosis, bicarbonate low → insulin stops letting potassium into cells, potassium acts as buffer by letting hydrogen into cells → hyperkalemia → ultimately lost in urine
- Dehydration (individual extremely thirsty), nausea, vomiting, mental status change
- Kussmaul respiration
 - Deep, labored breathing to move carbon dioxide out of blood
- Acetone breath
 - Ketone bodies break down into acetone → excrete as gas through lungs

DIAGNOSIS

LAB RESULTS

- Hyperkalemia ($> 5.2\text{mg/dl}$), initially with hypokalemia ($< 3.5\text{mg/dl}$)
- Glucose $> 250\text{mg/dL}$

Acid base status

- Ketones present in urine; arterial gas, bicarbonates measured; $\text{pH} < 7.3$

TREATMENT

MEDICATIONS

Insulin

- Lower blood glucose
- Monitor carefully
 - Rapid decrease in serum glucose → osmotic shift of water intracellularly → risk for cerebral edema → increased ICP
- Treat cerebral edema with hypertonic solution (3% saline, mannitol)

Fluid, electrolyte replacement

- 0.9% normal saline + potassium (KCl); serum K^+ levels drop as insulin shifts potassium intracellularly → risk for hypokalemia
- Bicarbonates
 - Reverse acidosis

OTHER INTERVENTIONS

- Fluids, rehydration



NOTES

ENDOCRINE TUMORS

GENERALLY, WHAT ARE THEY?

PATHOLOGY & CAUSES

- Tumors arising from endocrine gland tissue
- May be functional (excess secretion of one/more hormones); nonfunctional (clinically silent)

SIGNS & SYMPTOMS

- Depends on degree of hypersecretion, mass effect

DIAGNOSIS

DIAGNOSTIC IMAGING

CT scan/MRI

- Tumor visualization, staging

LAB RESULTS

- Measure hypersecretion degree

OTHER DIAGNOSTICS

- History, physical examination with characteristic findings

TREATMENT

MEDICATIONS

- Chemotherapy
- Hormone replacement/suppression

SURGERY

- Resection

OTHER INTERVENTIONS

- Radiation therapy
- Address complications

ADRENAL CORTICAL CARCINOMA

osms.it/adrenal-cortical-carcinoma

PATHOLOGY & CAUSES

- Rare, malignant adrenal cortex tumor
- Usually functional, with excess hormone secretion
 - Glucocorticoids → Cushing's syndrome
 - Androgens → virilization (biologically-female individuals), feminization (biologically-male individuals)
 - Aldosterone (rare) → hyperkalemia

RISK FACTORS

- Biologically female
- *Bimodal distribution*: ages 0–5, 40–50
 - *Adults*: more aggressive
- Associated with hereditary cancer syndromes (e.g. MEN1, Li-Fraumeni syndrome)

COMPLICATIONS

- Metastasis (renal vein, para-aortic nodes, lungs), diabetes

SIGNS & SYMPTOMS

- Rapidly progressing hypercortisolism signs
 - ↑ weight, muscle wasting, fat redistribution, skin atrophy
- Hyperandrogenism
 - **Female:** hirsutism, male-pattern baldness, oligomenorrhea
 - **Male:** gynecomastia, testicular atrophy, erectile dysfunction
- Mass effect
 - Abdominal, flank pain; nausea; vomiting

DIAGNOSIS

DIAGNOSTIC IMAGING

CT scan

- Usually unilateral, irregular shape, heterogeneous; presence of necrosis, calcification; tumor staging (local invasion/distant metastases)

LAB RESULTS

- Measure hypersecretion degree
 - Fasting blood glucose, potassium, basal cortisol, corticotropin (ACTH), 24-hour urinary free cortisol, sex hormones (e.g. dehydroepiandrosterone, androstenedione, testosterone, 17-hydroxyprogesterone, 17-beta-estradiol)

TREATMENT

MEDICATIONS

- Chemotherapy

SURGERY

- Resection

OTHER INTERVENTIONS

- Radiation therapy

PITUITARY ADENOMA

osms.it/pituitary-adenoma

PATHOLOGY & CAUSES

- Benign anterior pituitary tumor arising from specific cell types
 - Eventual normal pituitary tissue destruction → [hypopituitarism](#)
- Associated with genetic mutations
 - Loss-of-function mutations (*MEN1*)
 - Activating mutation in guanine nucleotide stimulatory protein (*Gs-alpha*)
 - Overexpression of pituitary tumor transforming gene (*PTTG*)
 - Expression of truncated form of fibroblast growth factor receptor (*FGF-4*)
- Monoclonal tumor formation → adjacent structure compression (e.g. meninges,

optic nerve/chiasm) + specific hormone hypersecretion

Classification

- **Microadenoma:** < 1cm/0.4in
- **Macroadenoma:** > 1cm/0.4in
- Functional, non-functional

TYPES

- Gonadotroph adenomas usually non-secreting/may cause hypogonadism
- Prolactinomas → hyperprolactinemia, galactorrhea, hypogonadism
 - [Lactotroph/somatotroph](#) adenoma (rare plurihormonal adenomas) secrete prolactin, growth hormone (GH)
- [Somatotroph](#) adenomas secrete GH → [acromegaly](#) (adults); [gigantism](#) (children)
- [Corticotropin](#) (adrenocorticotrophic hormone)

[ACTH)]-secreting adenomas → Cushing's syndrome

- Thyrotropin-secreting tumors → hyperthyroidism

RISK FACTORS

- Genetic predisposition, sporadic development

COMPLICATIONS

- Mass effect, pituitary apoplexy (hemorrhage into pituitary), sella turcica erosion, hormone-related disease development (e.g. Cushing syndrome), panhypopituitarism

SIGNS & SYMPTOMS

- Adjacent structure compression
 - Visual changes (e.g. diplopia, bitemporal hemianopsia), headache

DIAGNOSIS

DIAGNOSTIC IMAGING

Gadolinium-enhanced MRI

- Delineates tumor boundary; proximity to optic chiasm, cavernous sinus; tumor consistency; hemorrhage/cystic lesion presence
 - T1-weighted: hypointense
 - T2-weighted: hyperintense

LAB RESULTS

- Pituitary hormone hyper-/hyposecretion

TREATMENT

MEDICATIONS

- Replacement hormones (e.g. hydrocortisone, synthroid for hypopituitarism)
- Hormone suppression (e.g. somatostatin analogs for GH-secreting hormones; dopamine agonists for lactotrophs)

SURGERY

- Transsphenoidal tumor resection
- Stereotactic radiosurgery (gamma knife)

OTHER INTERVENTIONS

- Radiation therapy

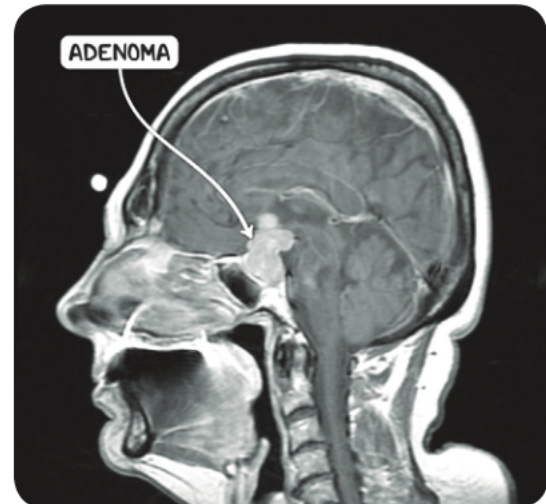


Figure 15.1 An MRI scan of the head in the sagittal plane demonstrating a large pituitary adenoma.

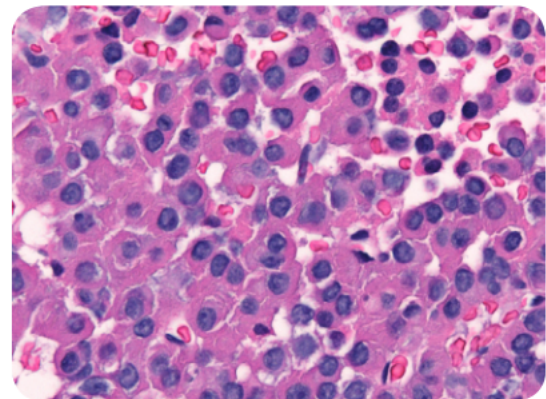


Figure 15.2 The histological appearance of a pituitary adenoma. The finely granular eosinophilic cytoplasm seen here is characteristic of a growth hormone producing adenoma. The lobular architecture of normal pituitary tissue is lost.

PROLACTINOMA

osms.it/prolactinoma

PATHOLOGY & CAUSES

- Functional, usually benign lactotroph cell tumor in anterior pituitary → prolactin (PL) secretion, prolactinemia
 - **Rarely:** tumors arise from both lactotroph, somatotroph cells → secrete growth hormone (GH), and PL
 - Malignant pituitary PRL-secreting carcinomas (rare)
- Monoclonal tumor formation → adjacent structure compression (e.g. meninges, optic nerve/chiasm) + prolactin hypersecretion → milk production stimulation; secondary gonadal function effects

Classification

- **Microadenoma:** < 1cm/0.4in
- **Macroadenoma:** > 1cm/0.4in

RISK FACTORS

- Biologically female
- Peak incidence during childbearing years
- May be associated with MEN1

COMPLICATIONS

- Hypothalamic-pituitary stalk compression → hypopituitarism
- Gonadal steroidogenesis impairment → infertility
- Hypogonadism-induced ↓ bone-mineral density → osteoporosis (biologically-female individuals)
- Male/female infertility

SIGNS & SYMPTOMS

- Microprolactinomas may be asymptomatic
- **Biologically-female individuals:** galactorrhea, amenorrhea, vaginal dryness
- **Biologically-male individuals:** gynecomastia, erectile dysfunction
- Mass effects → visual problems, headaches

DIAGNOSIS

DIAGNOSTIC IMAGING

Gadolinium-enhanced MRI

- Delineates tumor boundary; proximity to optic chiasm, cavernous sinus; tumor consistency; hemorrhage/cystic lesion presence

LAB RESULTS

- ↑ serum prolactin

TREATMENT

MEDICATIONS

- Dopamine agonists

SURGERY

- Transsphenoidal resection
- Stereotactic radiosurgery (gamma knife)

OTHER INTERVENTIONS

- Radiation therapy

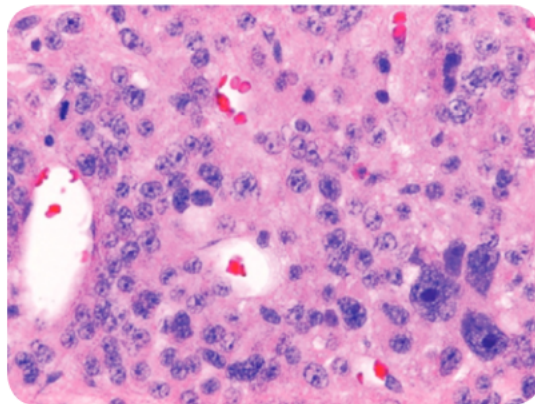


Figure 15.3 The histological appearance of a prolactinoma. The cells have moderate amounts of eosinophilic cytoplasm and finely granular nuclear chromatin.

THYROID CANCER

osms.it/thyroid-cancer

PATHOLOGY & CAUSES

- Uncommon thyroid gland carcinoma
- **Predominance:** biologically-female adults
- Derived from thyroid's follicular epithelium
 - Except medullary thyroid carcinoma → functional parafollicular C cells

TYPES

Papillary thyroid

- Most common, least aggressive
- Multiple projections arise from follicular cells growing towards blood vessels, lymphatics; papillae = small projection/outgrowth
 - Lymphatic spread to cervical lymph nodes
- May be part of inherited syndrome (Cowden syndrome, Gardner syndrome)
- Light microscopy
 - Cells with empty nuclei, AKA "Orphan Annie eyes"

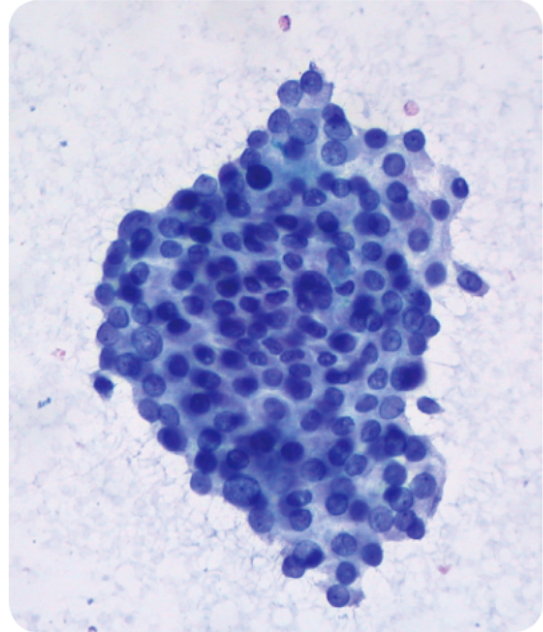


Figure 15.4 The cytological appearance of papillary thyroid carcinoma following fine needle aspiration. There are large cell clusters in a papillaroid configuration. The cell nuclei are of variable size.

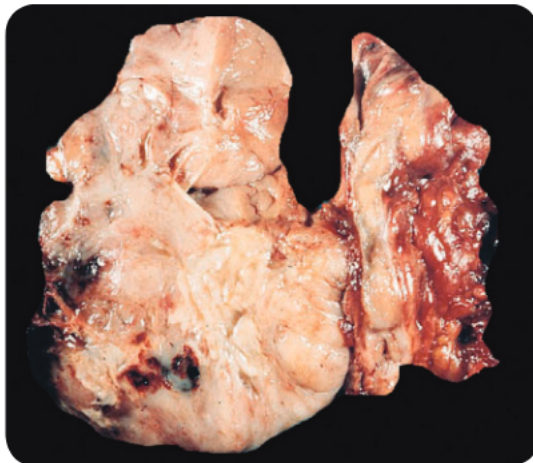


Figure 15.5 The gross pathological appearance of an anaplastic thyroid carcinoma which has replaced an entire thyroid lobe.

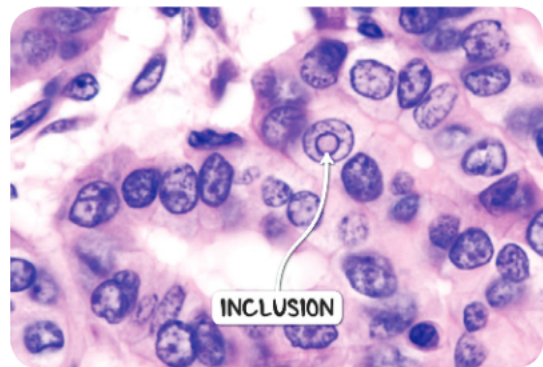


Figure 15.6 The histological appearance of thyroid papillary carcinoma at high magnification demonstrating nuclear inclusion bodies and pale chromatin with a dark nuclear envelope giving the classic orphan Annie appearance.

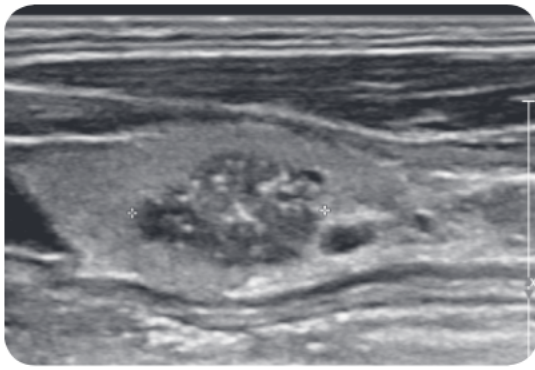


Figure 15.7 An ultrasound image of the left lobe of the thyroid demonstrating a papillary carcinoma. The tumor is well circumscribed and hypoechoic with visible microcalcifications.

Follicular thyroid

- AKA follicular adenocarcinoma; second most common
- Follicular cell invasion of thyroid capsule → blood vessel invasion → hematogenous spread to bone, liver, brain, lungs
 - Distant metastasis in some cases
- Well-circumscribed single nodules with colloid filled follicles; may be calcified, have central fibrosis
- May present with eosinophilic cells with granular cytoplasm; AKA Hürthle cells

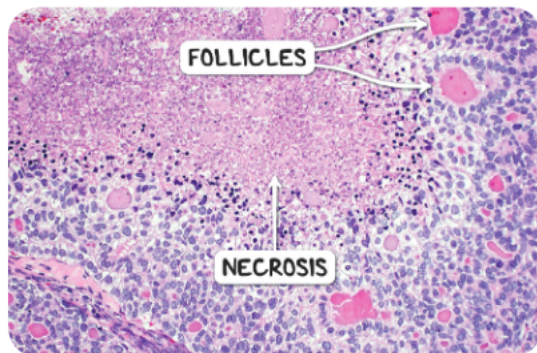


Figure 15.9 The histological appearance of follicular thyroid carcinoma. The tumor cells form vague follicular structures and there is abundant central necrosis.

Medullary thyroid carcinoma

- Arises from functional parafollicular C cells; in upper 1/3 of gland
 - Calcitonin secretion → breakdown → deposits in extracellular thyroid space → amyloid
- 1/3 familial, 1/3 sporadic, 1/3 associated with MEN 2A, 2B
- Germline RET mutations → abnormal receptor activation → cancer
- Light microscopy
 - Spindle shaped cells; amyloid deposits

Anaplastic/undifferentiated carcinomas

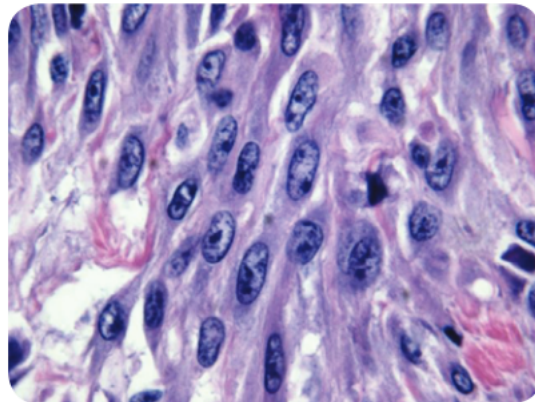


Figure 15.8 The histological appearance of a spindled anaplastic thyroid carcinoma.

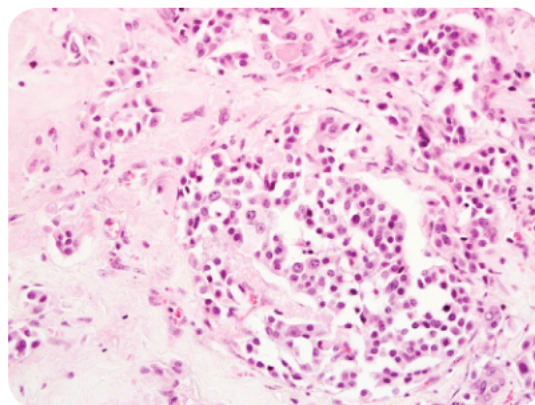


Figure 15.10 The histological appearance of medullary thyroid cancer. The nuclear chromatin displays a classic salt and pepper pattern.

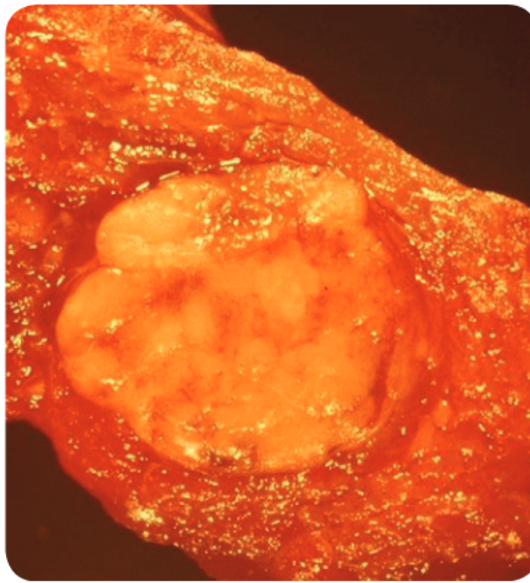


Figure 15.11 The gross pathological appearance of medullary carcinoma of the thyroid gland. The tumor is well circumscribed occupying a single thyroid lobe with a fleshy cut surface.

CAUSES

- Gain-of-function mutations in growth factor signaling pathways
 - Except medullary thyroid carcinoma

RISK FACTORS

Papillary thyroid

- *Childhood ionizing radiation exposure:* ionizing radiation → RET + BRAF proto-oncogene activation → cancer

Follicular thyroid

- *Iodine deficiency:* RAS, PIK3CA proto-oncogene activation + PTEN tumor suppressor gene inactivation → cancer

SIGNS & SYMPTOMS

- Large, solitary, painless, thyroid nodule (hard consistency, fixed)
- May impair thyroid hormone production → hypothyroidism
 - Weight gain, fatigue, cold intolerance
- Mass effect
 - Hoarseness, trouble swallowing

DIAGNOSIS

DIAGNOSTIC IMAGING

Ultrasound

- Thyroid
 - Solid vs. cystic thyroid nodule (most cancers solid)

LAB RESULTS

- Thyroid hormone levels

Fine needle aspiration

- Confirm diagnosis (benign vs. malignant)

Thyroid scan

- When fine needle aspiration indeterminate

TREATMENT

SURGERY

- Resection, adjuvant treatment



NOTES

GONADAL DYSFUNCTION

GENERALLY, WHAT IS IT?

PATHOLOGY & CAUSES

- Disturbance in gonadal development/function due to gonadal disorder/hypothalamic-gonadal axis dysfunction

CAUSES

- Impaired gonadal hormone production due to enzyme deficiency/receptor disturbance/exogenous hormone use
- Hypogonadotropic hypogonadism (AKA central/secondary hypogonadism)
 - Deficient gonadal hormone production due to decreased gonadotropin production
 - Gonadotropins, gonadal hormone levels low
- Hypergonadotropic hypogonadism (AKA peripheral/primary hypogonadism)
 - Deficient gonadal hormone production due to disease of gonads
 - Gonadotropin levels high, gonadal hormone levels low

RISK FACTORS

- Genetic (autosomal dominant disease), history (gestational diabetes)
- Environment (e.g. obesity, lack of physical exercise, steroid use)

COMPLICATIONS

- Most commonly leads to infertility

SIGNS & SYMPTOMS

- Individuals who are biologically male
 - *Primary sex characteristic dysfunction*: small penis, testes; improper testicular descent; low sperm count
 - *Secondary sex characteristic dysfunction*: lack of facial, body hair; low muscle mass; failure of voice mutation
- Individuals who are biologically female
 - *Primary sex characteristic dysfunction*: amenorrhea (absence of menstruation), oligomenorrhea (irregular menstrual cycle)
 - *Secondary sex characteristic dysfunction*: lack of breast development, pubic hair

DIAGNOSIS

LAB RESULTS

- Blood tests
 - Gonadotropic, gonadal hormone levels

OTHER DIAGNOSTICS

- Tanner scale
 - Identify delayed development
 - Development of primary, secondary sex characteristics divided into five stages based on pubic hair, testicular volume, breast development

TREATMENT

OTHER INTERVENTIONS

- Hormone replacement therapy
- Infertility treatments

5-ALPHA-REDUCTASE DEFICIENCY

osms.it/5-alpha-reductase_deficiency

PATHOLOGY & CAUSES

- Autosomal recessive sex-limited genetic mutation in *SRD5A2* gene (encodes enzyme 5 alpha reductase)
- Defective/absent
- Affects only individuals who are biologically male
- Defective 5 alpha reductase → ↓ testosterone to dihydrotestosterone conversion → impaired secondary sexual characteristics development

COMPLICATIONS

- Infertility; inflammation, infection of gonads due to malformation

SIGNS & SYMPTOMS

Pre-puberty

- Male internal sex organs present, external genitalia with female appearance
 - Phallus doesn't fully elongate; resembles something between clitoris, penis
 - *Bifid scrotum*: scrotum remains split
 - *Hypospadias*: urethral opening remains on underside of penis
 - *Ambiguous genitalia*: external genitalia does not look clearly male/female

Puberty

- ↑ testosterone → despite no testosterone conversion, phallus, scrotum grow larger → male appearance, deepening of voice, muscle growth, development of facial, body hair

DIAGNOSIS

LAB RESULTS

- Genetic testing
 - Karyotyping to ensure individual genetically male; confirm enzyme deficiency
- Normal serum testosterone level, ↓ dihydrotestosterone levels, ↑ testosterone to dihydrotestosterone ratio

OTHER DIAGNOSTICS

- Suspected in newborns with ambiguous genitalia

TREATMENT

MEDICATIONS

- Hormone replacement therapy
 - Male/female sex hormones according to gender role adopted by individual

SURGERY

- Surgical procedures to help restore external genitalia to nonambiguous appearance

OTHER INTERVENTIONS

- Assisted reproduction techniques
 - Internal genitalia do not produce ova, may produce sperm

ANDROGEN INSENSITIVITY SYNDROME

osms.it/androgen-insensitivity

PATHOLOGY & CAUSES

- Genetic disorder of defective androgen receptor gene
- Person with XY genotype unresponsive to androgens
- Inherited in X-linked recessive pattern

TYPES

- Complete androgen insensitivity
 - Completely nonfunctional receptor; cells do not respond to androgens at all
- Partial androgen insensitivity
 - Some remaining function of androgen receptor; cells, tissues partially sensitive to androgens
- Mild androgen insensitivity
 - Masculinization of external genitalia

CAUSES

- Defect in androgen receptor on external genitalia, genital ducts, testes itself

COMPLICATIONS

- Infertility (most cases)
- Risk of testicular cancer due to cryptorchidism in complete androgen insensitivity

SIGNS & SYMPTOMS

Complete androgen insensitivity

- Cryptorchidism
 - Without effects of androgens, testes fail to descend into scrotum, remain in abdomen/pelvis
- Ineffective spermatogenesis
 - Epididymis, vas deferens, seminal vesicles do not develop normally

- Development of female secondary sex characteristics
 - Excess testosterone converted into estrogen → breast growth, widening of hips, female fat distribution
- Failed development of internal female organs
 - Testes still produce anti-Müllerian hormone → uterus, fallopian tubes do not develop, vagina ends in blind pouch → female appearance without menstrual cycles

Partial androgen insensitivity

- Appearance of external genitalia, secondary sex characteristics varies widely

Mild androgen insensitivity

- Masculinization of external genitalia, some female secondary sex characteristics

DIAGNOSIS

DIAGNOSTIC IMAGING

Ultrasound

- Absence of uterus, ovaries; cryptorchidism

LAB RESULTS

- ↑ serum testosterone, dihydrotestosterone
- Genetic testing
 - Karyotype; visualize sex chromosomes, ensure individual genetically male

OTHER DIAGNOSTICS

- Diagnosed in infants with cryptorchidism
- Can remain undiagnosed until puberty

TREATMENT

MEDICATIONS

- Hormone replacement therapy
 - Male/female sex hormones according to gender role adopted by individual; testosterone/dihydrotestosterone if male, estrogen if female

SURGERY

- Surgical removal of testes (esp. in cryptorchidism) to reduce cancer risk
- External genitalia correction

DELAYED PUBERTY

osms.it/delayed-puberty

PATHOLOGY & CAUSES

- Onset of puberty after age 13 in individuals who are biologically female, after 14 in individuals who are biologically male

TYPES

Primary/hypogonadotropic hypogonadism

- Dysfunction of gonads due to unresponsiveness to luteinizing hormone (LH), follicle-stimulating hormone (FSH)/lack of testosterone/estrogen, progesterone production in gonads → no negative feedback on hypothalamus → overproduction of LH, FSH
- Causes of acquired
 - Radiation therapy, chemotherapy, trauma to gonads
- Causes of congenital
 - **Klinefelter syndrome**: two X chromosomes in individuals who are biologically male → small testes, sterility
 - **Turner syndrome**: X chromosome missing in individuals who are biologically female → dependence on hormonal treatment to develop secondary sex characteristics

Secondary/ hypogonadotropic hypogonadism

- Hypothalamus/pituitary gland dysfunction; inability to produce gonadotropin-releasing hormone (GnRH)/LH, FSH; suppression

from other hormones (e.g. prolactin, thyroid hormone)

- Causes of acquired
 - Radiation therapy, chemotherapy, trauma to gonads, tumor of pituitary gland, hypothalamus
- Causes of congenital
 - **Kallmann syndrome**, panhypopituitarism
- General causes
 - Chronic illness (e.g. cystic fibrosis, celiac disease), excessive exercise, malnutrition/obesity, stress; affect hypothalamus, pituitary release of hormones

Constitutional delay

- Temporary delay in puberty; doesn't typically result in infertility
- Lack of GnRH, not pathologic → naturally slowed rate of maturation
- Onset of puberty occurs naturally, at later age; typically genetic component

COMPLICATIONS

- Permanent infertility if puberty never begins/fails to complete, sexual maturity never reached

SIGNS & SYMPTOMS

- Delayed primary, secondary sexual characteristics

DIAGNOSIS

LAB RESULTS

- Blood hormone levels
 - Indicate type of hypogonadism; ↓ testosterone, estrogen in low gonad activity; ↓ FSH, LH in suppressed pituitary activity

OTHER DIAGNOSTICS

- Medical history
 - Evaluate underlying medical conditions, family history for constitutional delay
- Tanner scale
 - Estimates puberty development

TREATMENT

MEDICATIONS

- Hormone replacement therapy

OTHER INTERVENTIONS

- Constitutional delay can resolve on own with natural onset of puberty
- Infertility treatments

KALLMANN SYNDROME

osms.it/kallmann-syndrome

PATHOLOGY & CAUSES

- Type of hypogonadotropic hypogonadism; delayed/absent puberty with impaired sense of smell (anosmia)
- Pituitary failure → ↓ sex hormones → hypogonadotropic hypogonadism → failure to start/complete puberty
- Defect in migration of neurons from olfactory placode
 - **Olfactory neurons:** hyposmia/anosmia (reduced sense of smell)
 - **GnRH neurons:** ↓ GnRH → ↓ LH, FSH

COMPLICATIONS

- Infertility, osteopenia, osteoporosis

SIGNS & SYMPTOMS

- Underdevelopment of primary, secondary sex characteristics; anosmia; long arms in proportion to body (eunuchoid body); osteoporosis; kidney agenesis
- Skeletal
 - Scoliosis, short middle finger, split hand/

foot, teeth underdevelopment, cleft palate

- Neurological sensory, motor
 - Hearing impairment, colour blindness, dyskinesias, cerebral ataxia

DIAGNOSIS

LAB RESULTS

- Blood hormone levels
 - ↓ GnRH, LH, FSH, sex hormones
- Genetic tests
 - Gene mutation in *FGFR1*, *PROKR2*, *PROK2*, *CHD7*, *FGF8*; associated with Kallmann syndrome

OTHER DIAGNOSTICS

- Smell test, sperm count

TREATMENT

MEDICATIONS

- Hormone therapy
 - Stimulate puberty, development of secondary sex characteristics

- Calcium, vitamin D
 - Osteopenia

OTHER INTERVENTIONS

- Infertility treatments

POLYCYSTIC OVARY SYNDROME

osms.it/polycystic-ovary

PATHOLOGY & CAUSES

- Excessive androgen production by ovaries; primarily testosterone

CAUSES

Hyperinsulinemia

- Aids LH overproduction
- Theca cells in ovary express insulin receptors → excess insulin induces growth, division of theca cells → ↑ LH receptors → hypothalamus ↑ rate of GnRH pulses → ↑ LH secretion

Anterior pituitary produces excessive LH

- Theca cells produce excess amounts of androstenedione → converted into estrone by aromatase in adipose tissue → negative feedback signal → blocks anterior pituitary from releasing FSH, LH → no LH surge → no dominant follicle to break away from ovary → remains in ovary as cyst/ degenerates with other follicles → no ovulation

Excessive adipose tissue

- Aromatase in adipose tissue converts androgens to estrogens → ↑ androgens

RISK FACTORS

- Genetic: autosomal dominant disease
- Obesity, lack of physical exercise
- History of gestational diabetes

COMPLICATIONS

- Diabetes mellitus, hyperinsulinemia, infertility, increased risk of endometrial cancer

SIGNS & SYMPTOMS

- High levels of androstenedione → virilization
 - Excessive hair growth on chin, upper lip, chest, back (hirsutism)
 - Thinning of hair, from crown of head (male-pattern baldness)
 - Acne on face, chest, back
 - Lack of ovulation → oligomenorrhea, amenorrhea → infertility
- Insulin resistance
 - Overweight/obese; dark, velvety patches in creases of neck, groin, underarms (acanthosis nigricans)

DIAGNOSIS

DIAGNOSTIC IMAGING

Ultrasound

- Follicles on one/both ovaries, appear like small cysts

LAB RESULTS

- Blood tests
 - ↑ LH to FSH ratio; ↑ androstenedione

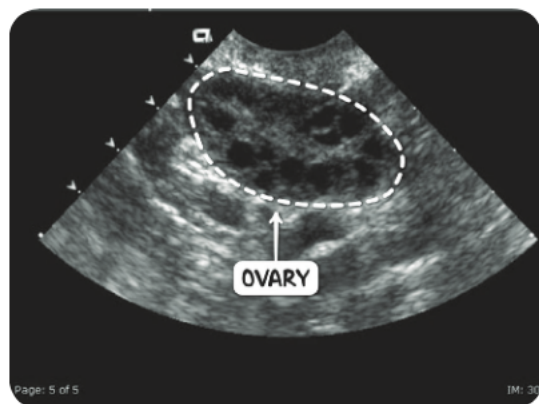


Figure 16.1 An abdominal ultrasound scan demonstrating a polycystic ovary. The cysts are represented by the well circumscribed hypoechoic areas within the ovary.

OTHER DIAGNOSTICS

- Rotterdam criteria (2 of 3)
 - Lack of ovulation, excessive androgens, polycystic ovaries on ultrasound
- Oral glucose tolerance test (OGTT)
 - Establish insulin resistance

TREATMENT

MEDICATIONS

- Oral contraceptives
 - Regulate menstrual cycle
- Clomiphene citrate
 - Induce ovulation
- Metformin
 - Increase insulin sensitivity

SURGERY

- Ovarian drilling
 - Puncturing cystic ovary; induces ovulation; can damage ovary, doesn't resolve overall hormonal imbalance

OTHER INTERVENTIONS

- Incurable condition, treatment symptoms
- **Weight loss**, low glycemic index diet reduces insulin resistance, improves symptoms

PRECOCIOUS PUBERTY

osms.it/precocious-puberty

PATHOLOGY & CAUSES

- Onset of puberty at earlier age than average
 - \leq eight in individuals who are biologically female, \leq nine in individuals who are biologically male

chorionic gonadotropin (hCG); infection; cyst; radiation damage to brain \rightarrow impairs negative feedback system in hypothalamic-pituitary-gonadal axis

- **Idiopathic precocious puberty**: most common; normal variation; depends on weight, genetics

TYPES

Central/gonadotropin-dependent precocious puberty

- Early maturation of hypothalamic-pituitary-gonadal axis \rightarrow early release of LH, FSH \rightarrow \uparrow sex hormones
- Cause
 - **Dysfunctional hypothalamus/pituitary gland**: tumor releases GnRH/human

Peripheral/gonadotropin-independent precocious puberty

- Abnormal overproduction of sex hormones by testes/ovaries
- Cause
 - Ovarian/testicular cyst/tumor; genetic conditions (e.g. McCune–Albright syndrome); dysfunction of other glands (thyroid/adrenal gland); exogenous sex hormones from medications, creams

SIGNS & SYMPTOMS

- Child starts progressing through Tanner scale before 95% of other children at same age
- Early sexual maturation

DIAGNOSIS

DIAGNOSTIC IMAGING

MRI

- Structural abnormalities in brain

Ultrasound

- Screening of gonads

X-ray

- Estimates bone maturation

LAB RESULTS

- Gonadotropin hormone levels
 - Distinguish gonadotropin-dependent/independent causes

OTHER DIAGNOSTICS

- Physical exam
 - Assess growth compared to age; Tanner scale

TREATMENT

MEDICATION

- Hormone therapy
 - GnRH analogues → suppress hypothalamic-pituitary-gonadal axis hormones, bind to GnRH receptor on pituitary gland → decrease release of LH, FSH → slow puberty

SURGERY

- Surgical removal of tumor/cyst from ovaries/testicles

PREMATURE OVARIAN FAILURE

osms.it/premature-ovarian-failure

PATHOLOGY & CAUSES

- AKA primary ovarian insufficiency
- Loss of function of ovaries before age 40; not caused by menopause
- Follicles stop responding to pituitary LH, FSH → disrupted ovulation → ↓ estrogen, progesterone, androstenedione → amenorrhea, hypogonadotropism, hypoestrogenism
- Around half of biologically-female individuals maintain some intermittent ovarian function
- Usually no clear cause; associated with
 - Acquired: chemotherapy, radiotherapy, autoimmune destruction
 - Genetic: Turner syndrome, fragile X syndrome, BRCA1 mutations →

gonadal dysgenesis

- Two mechanisms
 - No remaining follicles: ovary started off with few/rapid degeneration
 - Follicles dysfunctional: hypergonadotropic hypogonadism; estrogen-low pituitary increases LH, FSH production

COMPLICATIONS

- Infertility, cardiovascular disease, osteoporosis, hypothyroidism, Addison's disease

SIGNS & SYMPTOMS

- Absence of ovulation; low levels of estrogen, progesterone
- Normal puberty with regular periods before disorder develops
- Infrequent menstrual periods → difficulty conceiving/infertility
- **Lack of hormones:** hot flashes, night sweats, vaginal dryness → dyspareunia (pain during sex)
- ↓ **estrogen:** cardiovascular disease, osteoporosis, decreased bone density
- Symptoms mimic natural menopause; some biologically-female individuals still able to get pregnant due to intermittent ovarian function

DIAGNOSIS

DIAGNOSTIC IMAGING

Ultrasound

- Shrunken ovaries

LAB RESULTS

- ↓ ovarian hormones (estrogen), ↑ LH, FSH
- If autoimmune cause suspected
 - Test for steroid cell antibodies/sulfoxythiocarbamate alkynes (STCAs)
- **Genetic testing**
 - Karyotype, chromosomal abnormalities; evaluate for genetic disease

TREATMENT

MEDICATIONS

- Hormone replacement therapy
 - Estrogen, progesterone

OTHER INTERVENTIONS

- In-vitro fertilization
 - Treat infertility



NOTES

HYPERPARATHYROIDISM & HYPOPARATHYROIDISM

GENERALLY, WHAT ARE THEY?

PATHOLOGY & CAUSES

- An imbalance of parathyroid hormone (PTH) due to overproduction or underproduction by the parathyroid gland resulting in impaired regulation of calcium and other electrolytes

Hyperparathyroidism

- \uparrow PTH \rightarrow \uparrow bone resorption and \uparrow renal reabsorption of calcium \rightarrow \uparrow serum calcium levels \rightarrow asymptomatic or symptomatic hypercalcemia

Hypoparathyroidism

- \downarrow PTH \rightarrow \downarrow serum calcium \rightarrow symptomatic hypocalcemia

RISK FACTORS

- Hyperparathyroidism
 - Genetic mutations, chronic kidney disease, \downarrow vitamin D intake/absorption, hyperplasia of parathyroid glands
- Hypoparathyroidism
 - Most commonly iatrogenic cause due to accidental removal or damage to parathyroid blood supply during thyroid surgery

COMPLICATIONS

- Hyperparathyroidism
 - Osteoporosis, osteitis fibrosa cystica, nephrolithiasis, keratopathy, symptomatic hypercalcemia (e.g. hypertension, cardiac arrhythmias)
- Hypoparathyroidism
 - Symptomatic hypercalcemia (e.g. respiratory paralysis, cardiac arrhythmias)

SIGNS & SYMPTOMS

- See individual disorders

DIAGNOSIS

LAB RESULTS

- Measure serum PTH, calcium, phosphate, magnesium, 25-hydroxyvitamin D, urine calcium

OTHER DIAGNOSTICS

- Genetic testing

TREATMENT

MEDICATIONS

- Hyperparathyroidism
 - Vitamin D analogs, calcimimetics, bisphosphonates
- Hypoparathyroidism
 - IV calcium gluconate (acute), vitamin D analogs, synthetic PTH, thiazide diuretics (\downarrow renal calcium excretion)

SURGERY

- Hyperparathyroidism
 - Partial/complete parathyroidectomy; radiofrequency ablation

OTHER INTERVENTIONS

- Hyperparathyroidism
 - Physical activity to \downarrow bone resorption, maintain hydration to \downarrow nephrolithiasis, vitamin D supplements
- Hypoparathyroidism
 - Calcium, magnesium, and vitamin D supplements

HYPERPARATHYROIDISM

osms.it/hyperparathyroidism

PATHOLOGY & CAUSES

TYPES

Primary

- Parathyroid gland creates PTH independently of calcium levels, does not respond to normal feedback mechanisms

Secondary

- Parathyroid gland hyperplasia, excess parathyroid hormone secreted in response to chronic hypocalcemia
- Impaired kidney function; kidneys do not filter phosphate properly into urine, make insufficient calcitriol
 - AKA renal osteodystrophy (bone pain, fracture)
- Altered calcium, phosphate levels → increased parathyroid hormone levels → bone resorption

Tertiary

- Develops in individuals with secondary hyperparathyroidism for many years, often due to hyperplasia of parathyroid glands
- Autonomous secretion of PTH separately from blood calcium levels
 - Even if causes of secondary hyperparathyroidism (e.g. renal transplant) corrected, increased PTH persists

RISK FACTORS

Primary

- Genetic mutations
 - Multiple endocrine neoplasia (MEN) syndrome

COMPLICATIONS

Primary

- Brown tumors, large bone cysts (due to high osteoclast activity)

SIGNS & SYMPTOMS

- "Stones, thrones, bones, groans, and psychiatric overtones"; see mnemonic

Primary, tertiary

- Slower muscle contractions caused by less excitable neurons secondary to hypercalcemia

Secondary

- Bone resorption/renal osteodystrophy; calcification of blood vessels, soft tissues



MNEMONIC

Signs and symptoms of hyperparathyroidism

Stones: calcium-based kidney stones, gallstones

Thrones: toilet; polyuria (frequent urination) from impaired sodium, water reabsorption

Bones: pain from chronic hormone-driven demineralization

Groans: constipation, muscle weakness

Psychiatric overtones: depressed mood, confusion

DIAGNOSIS

LAB RESULTS

Primary

- High total serum calcium (hypercalcemia), low phosphate (hypophosphatemia), high PTH value during diastole
- Hypercalciuria from excess calcium loss through urine, may cause dehydration
- Serum 25-hydroxyvitamin D
 - Determine type

Secondary

- Low calcium, high phosphate, low vitamin D

Tertiary

- Normal-high calcium, high PTH, low vitamin D

TREATMENT

MEDICATIONS

Primary, tertiary

- Calcimimetics
 - Drugs that imitate calcium by attaching to CaSR on parathyroid cells
 - If surgery not an option

Secondary

- Hyperphosphatemia
 - Phosphate binders
- Vitamin D supplements
 - Increase calcium absorption, reduce PTH synthesis
- Calcitriol, vitamin D analogs (doxercalciferol, paricalcitol)
 - Suppress PTH levels
- Calcimimetics
 - Modulate CaSR → increase sensitivity of serum calcium → decrease PTH levels

Tertiary

SURGERY

- Remove abnormal parathyroid glands

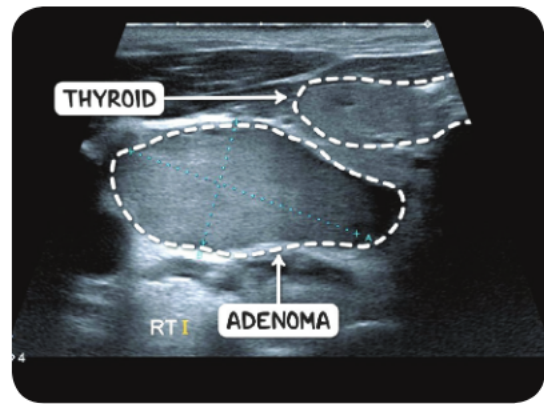


Figure 17.1 An ultrasound of the neck demonstrating a large parathyroid adenoma situated posteriorly and to the right of the right thyroid lobe. The skin surface is at the top of the image.

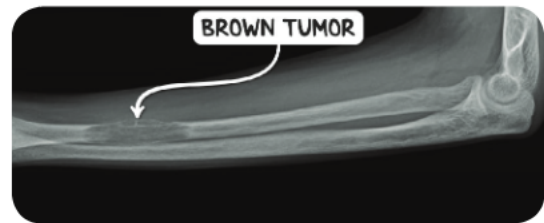


Figure 17.2 A X-ray image of the forearm demonstrating a brown tumor of the distal radius in an individual with hyperparathyroidism.

HYPERPARATHYROIDISM LABS

	SERUM CALCIUM	SERUM PHOSPHATE	PARATHYROID HORMONE
PRIMARY HYPERPARATHYROIDISM	High	Low	High
SECONDARY HYPERPARATHYROIDISM	Low	High	High
TERTIARY HYPERPARATHYROIDISM	High	Varies	High

HYPOPARATHYROIDISM

osms.it/hypoparathyroidism

PATHOLOGY & CAUSES

- Underproduction of parathyroid hormone (PTH); hypo- = under/low
- No parathyroid hormone → ↓ bone resorption, ↓ renal calcium reabsorption, ↓ intestinal calcium reabsorption → hypocalcemia, hyperphosphatemia → ↑ cell excitability → tetany, paresthesias, seizures, arrhythmias

CAUSES

Autoimmune disorders

Magnesium deficiencies

Latrogenic

- Most common
- Thyroid/parathyroid surgery/radiation

Hereditary abnormalities

- DiGeorge syndrome (DGS)
- Autosomal dominant hypoparathyroidism
- Albright hereditary osteodystrophy (pseudohypoparathyroidism)
 - Kidney resistance to PTH, increased PTH

SIGNS & SYMPTOMS

- Asymptomatic/life-threatening
 - Degree, duration of hypocalcemia
 - Muscular dysfunction → respiratory paralysis → death
- ECG changes
 - Prolonged QT, ST
 - Torsades des pointes
 - Atrial fibrillation

Acute

- Muscular spasms/cramps → tetany → Chvostek, Trousseau signs
- Perioral numbness, paresthesias, seizures

Chronic

- Extrapyramidal movements → basal ganglia calcifications
 - Dystonias, parkinsonism, athetosis, hemiballismus, oculogyric crisis
- Cataracts
- Dermatologic manifestations
 - Dry, coarse skin; brittle nails; patchy alopecia



Figure 17.3 Dry, brittle nails are a dermatologic manifestation of chronic hypoparathyroidism.

DIAGNOSIS

LAB RESULTS

- Hypocalcemia, low serum PTH
- Hypercalciuria

OTHER DIAGNOSTICS

- Medical history of thyroid surgery/radiation

TREATMENT

MEDICATIONS

- IV calcium gluconate (severe cases)
- Oral calcium (mild-moderate cases)
- Vitamin D supplementation
- Synthetic PTH



NOTES

HYPERPITUITARISM & HYPOPITUITARISM

GENERALLY, WHAT ARE THEY?

PATHOLOGY & CAUSES

- Disorders caused by excess/insufficient pituitary hormones, disruption in hypothalamic-pituitary axis function

CAUSES

Hyperpituitarism

- Genetic inheritance
- Secreting tumors (intracranial, ectopic)

Hypopituitarism

- Intracranial tumors, bleeding, infarction
- Neurosurgery, head trauma, infection
- Idiopathic

SIGNS & SYMPTOMS

- Disruption in growth, regulation; depends on affected hormones
- If pituitary adenoma, sequence of loss: "Go Look For The Adenoma" (see mnemonic)



MNEMONIC: Go Look For The Adenoma

Pituitary adenoma sequence of loss

- G**rowth hormone (GH)
- L**uteinizing hormone (LH)
- F**ollicle-stimulating hormone (FSH)
- T**hyroid-stimulating hormone (TSH)
- A**drenocorticotrophic hormone (ACTH)

DIAGNOSIS

DIAGNOSTIC IMAGING

X-ray, CT scan, MRI

- Intracranial, ectopic tumors; bleeding, infarction

LAB RESULTS

- Altered levels of pituitary, target tissue hormones

OTHER DIAGNOSTICS

- History, physical examination

TREATMENT

MEDICATIONS

Hyperpituitarism

- Somatostatin + dopamine agonists; GH receptor antagonists

Hypopituitarism

- Hormone replacement (e.g. glucocorticoids, thyroid hormone)

SURGERY

- Surgical excision of tumor

ACROMEGALY

osms.it/acromegaly

PATHOLOGY & CAUSES

- GH hypersecretion in adulthood after epiphyseal closure → enlargement of extremities, face

CAUSES

- Pituitary adenoma produces excess GH
- Nonpituitary tumors (pancreatic, lung, adrenal gland) produce ectopic GH

COMPLICATIONS

- Glucose intolerance to Type II diabetes, high blood pressure, respiratory problems, carpal tunnel syndrome, heart/kidney failure

SIGNS & SYMPTOMS

- Soft tissue, bone swelling
 - Hands, feet
 - **Skull:** jaw protrusion, enlargement (macrognathia), increased spacing of teeth; forehead, brow protrusion
 - **Organomegaly:** heart, kidneys; vocal cords → slow, deep voice
- Joint pain, headache, vision problems, thickened skin
- Excess sweating, hair growth, pigmentation

DIAGNOSIS

DIAGNOSTIC IMAGING

MRI of sella turcica with gadolinium

- Somatotroph adenoma; tumoral location

CT scan of chest/abdomen

- Ectopic tumors

LAB RESULTS

Blood tests

- Acromegaly
 - ↑ insulin-like growth factor-1 (IGF-1) / somatomedin C
- Oral glucose tolerance test (OGTT)
 - Hyperglycemia

TREATMENT

MEDICATIONS

- Somatostatin agonists
 - Stop GH production
- Dopamine agonists, alternative to somatostatin agonists
 - For tumors that affect prolactin levels
- GH receptor antagonists
 - Blocks GH binding to receptors

SURGERY

- Transsphenoidal tumor resection

OTHER INTERVENTIONS

- Tumor radiation



Figure 18.1 The clinical appearance of acromegaly. The facial features are coarse and mandibular overgrowth has led to prognathism.



Figure 18.2 The appearance of the hands in the case of acromegaly. The acromegalic right hand is larger with expanded soft tissues and thickened, stubby fingers.

CONSTITUTIONAL GROWTH DELAY

osms.it/constitutional-growth-delay

PATHOLOGY & CAUSES

- Normal variation in rate of growth → temporary delay during early childhood, puberty
- Eventual adult height within normal range

CAUSES

- Alterations in hormones critical for growth, development
- GH axis: regulates bone, muscle growth
- ↓ GH → ↓ production of IGF-1/ somatomedin C (prevents cell death), ↑ cellular metabolism, cell division, differentiation throughout body
- Hypothalamic-pituitary-gonadal axis: regulates sexual maturation
- ↓ gonadotropin-releasing hormone (GnRH) → ↓ anterior pituitary production of gonadotropins (LH, FSH) → ↓ production of sex hormones by gonads (estrogen, progesterone in individuals who are biologically female, testosterone in individuals biologically male) → delayed development of sex organs, secondary sexual characteristics

RISK FACTORS

- Family history of delayed growth

COMPLICATIONS

- Psychosocial stress

SIGNS & SYMPTOMS

- Normal size at birth
- Short preadolescent stature
- Delayed pubertal development, skeletal age

DIAGNOSIS

DIAGNOSTIC IMAGING

X-ray

- Delayed bone development

OTHER DIAGNOSTICS

- History, physical examination
- Height growth curve below, parallel to third percentile
- Delayed Tanner scale staging

TREATMENT

OTHER INTERVENTIONS

- Provide reassurance regarding eventual normal growth, development

DIABETES INSIPIDUS (DI)

osms.it/diabetes-insipidus

PATHOLOGY & CAUSES

- Disorder of fluid balance characterized by defect in urine concentration → excretion of large volumes of dilute urine
- Diabetes = to pass through; insipidus = tasteless

TYPES

Neurogenic (central) DI

- DI caused by absence/↓ secretion/production of antidiuretic hormone (ADH) by posterior pituitary

Nephrogenic DI

- Kidneys unresponsive to ADH secreted by posterior pituitary

CAUSES

Neurogenic DI

- Idiopathic (most common)
- Damage to hypothalamus/pituitary/supraoptic-hypophyseal tract (e.g. head trauma, pituitary adenoma), neurosurgery, infection (e.g. tuberculosis), infiltrative disease (e.g. Langerhans cell histiocytosis), hypoxic encephalopathy, ischemia
- Familial (familial neurohypophyseal DI)
 - Autosomal dominant gene mutation
- Congenital (e.g. septo-optic dysplasia)

Nephrogenic DI

- Hereditary
 - Defect in genes encoding for ADH receptor/aquaporin function

- Damage of renal tubules from systemic disease (e.g. polycystic kidney disease, pyelonephritis, amyloidosis)
- Lithium toxicity
 - Interferes with aquaporin function

SIGNS & SYMPTOMS

- Polyuria
 - **Neurogenic:** urine amount varies depending on degree of ADH production/secretion
 - **Nephrogenic:** daily output of > 3L in adults; > 2L/m² in children
- Nocturia, polydipsia, dehydration, hypotension
- Neurogenic DI
 - Lack of other pituitary hormones

DIAGNOSIS

DIAGNOSTIC IMAGING

Cranial MRI (neurogenic DI)

- Hyperintensities, pituitary stalk thickening identifies signs of hypothalamic/pituitary dysfunction

LAB RESULTS

- ↓ ADH levels (neurogenic), urine osmolality
- ↑ plasma osmolality
- Hypernatremia
- **Water deprivation test (ADH stimulation test):** fluid deprivation → ADH (vasopressin) administered subcutaneously

- ↑ **urine osmolality**: confirms neurogenic DI
- **Little/no** ↑ **urine osmolality**: confirms nephrogenic DI

TREATMENT

MEDICATIONS

Neurogenic DI

- Desmopressin (dDAVP) (synthetic vasopressin)
- Chlorpropamide
 - Enhances renal response to low levels of ADH

Neurogenic/nephrogenic DI

- Nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g. indomethacin)
 - ↑ renal concentration of urine
- Thiazide diuretics (e.g. hydrochlorothiazide) + low sodium diet
 - ↓ polyuria (↑ water permeability to collecting tubules)

OTHER INTERVENTIONS

- Fluid replacement
- Diet
 - Low solute (low sodium, low protein)

GIGANTISM

osms.it/gigantism

PATHOLOGY & CAUSES

- GH hypersecretion during childhood → rapid, excessive linear growth

CAUSES

- Excessive secretion of GH, GHRH, IGF-1
- Tumor in pituitary gland
- Tumors outside pituitary, secrete GH
- Hereditary
 - Gene mutation (e.g. McCune Albright syndrome, multiple endocrine neoplasia Type I)

COMPLICATIONS

- **Cardiovascular conditions**: hypertension in children
- **Bone conditions**: osteoarthritis
- **Diabetes mellitus**: insulin resistance

SIGNS & SYMPTOMS

- Height significantly above standard deviations
- Obesity

- Overgrowth of face, extremities
- Headaches
- Maxilla/mandible protrusion

DIAGNOSIS

DIAGNOSTIC IMAGING

MRI

- Pituitary tumors

CT scan

- Tumors in other organs, might secrete GH/ GHRH

X-ray

- Assess bones

LAB RESULTS

Blood tests

- OGTT
 - Hyperglycemia
 - Elevated IGF-1

TREATMENT

MEDICATIONS

- Somatostatin agonists
 - Shrink pituitary tumors, stop GH production
- Dopamine agonists
 - If somatostatin agonists not effective
 - Effective in tumors producing hyperprolactinemia
- Somatostatin + dopamine agonists
- GH receptor antagonists

SURGERY

- For small pituitary adenomas
 - Transsphenoidal surgical approach

OTHER INTERVENTIONS

- Radiation (not recommended for children)
 - Can produce panhypopituitarism (decreased secretion in most pituitary hormones) → learning disabilities, obesity



Figure 18.3 The worlds tallest ever recorded man, Robert Wadlow, was diagnosed with from gigantism as a consequence of pituitary hyperplasia. He stood at 2.27m/8ft 11in and wore a size 37 shoe.

GROWTH HORMONE DEFICIENCY (GHD)

osms.it/growth-hormone-deficiency

PATHOLOGY & CAUSES

- Conditions caused by decreased production of GH (AKA somatotropin)
- Partial/complete, permanent/transient

CAUSES

- Hypothalamic/pituitary dysfunction
 - Tumors (e.g. pituitary/parasellar adenomas); radiation; traumatic injury; autoimmune disease; genetic mutations (e.g. PROP1); congenital structural defects of brain (e.g. Prader-Willi, Turner syndrome); idiopathic

SIGNS & SYMPTOMS

- Newborns
 - Hypoglycemia, micropenis, excessive jaundice
- Children
 - Stunted growth/short stature, delayed puberty
 - Nystagmus, hypoglycemia, retinal defects, midfacial defects (e.g. cleft lip)
 - **Severe cases:** delayed basic motor skills (e.g. standing, walking)
 - Moderately overweight (rare—severely obese)
- Adults
 - Decreased muscle mass, decreased bone mineral density, high 5-alpha reductase, baldness, cardiac conditions
 - Psychological issues (memory problems, social issues, depression)

DIAGNOSIS

LAB RESULTS

- Serum GH levels < 1ng/mL
 - Nonspecific test for GH deficiency: affected by circadian rhythms, food intake, stress

- Serum IGF-1
 - More accurate assessment of GH secretion; not affected by external factors
 - Less than standard gender-specific levels → confirms diagnosis
- Insulin tolerance test
 - Regular insulin administered via intravenous (IV) → measure blood at 30 minute intervals
 - Subnormal increase in serum GH confirms diagnosis

TREATMENT

MEDICATIONS

- Daily injections with recombinant growth hormone (rGH)
 - **Childhood:** GH daily injections; stature monitoring throughout growth period
 - **Adulthood:** 25% treatment for children

HYPERPITUITARISM

osms.it/hyperpituitarism

PATHOLOGY & CAUSES

- Disorders caused by pituitary hormones hypersecretion

CAUSES

- Pituitary adenoma (most common)
- Genetic mutation from single cell (monoclonal) → tumorigenesis → tumor secretes hormones
 - Prolactin → prolactinoma
 - ACTH → Cushing's disease

- GH → acromegaly (occurs during adulthood after epiphyseal closure), gigantism (during childhood before epiphyseal closure)

SIGNS & SYMPTOMS

- Diaphoresis; visual field problems; headaches; lethargy; excessive hair growth; larger organs, extremities, facial components

DIAGNOSIS

DIAGNOSTIC IMAGING

X-ray

- Sella turcica, pituitary glands

LAB RESULTS

- Elevated hormone levels in serum

TREATMENT

MEDICATIONS

- Dopamine agonists: gonadal dysfunctions
 - Inhibit prolactin secretion
 - Inhibitors of tumoral cells division

SURGERY

- Total/partial removal of pituitary/tumor
 - Endonasal transsphenoidal surgery (most common)

HYPERPROLACTINEMIA

osms.it/hyperprolactinemia

PATHOLOGY & CAUSES

- Disorder caused by high blood levels of pituitary hormone prolactin
- **Prolactin:** secreted by lactotroph cells in anterior segment of pituitary

CAUSES

- Prolactinoma/lactotroph adenoma (prolactin-secreting tumor)
- Pregnancy
- Damage to hypothalamic-pituitary stalk
- Disorders affecting hypothalamus
- **Drugs,** medication, heavy metal poisoning
 - Inhibits dopamine production
 - Dopamine receptor antagonists, synthesis inhibitors → pituitary overproduces prolactin
- Renal failure
- Primary hypothyroidism

- Overdevelopment of mammary glands (gynecomastia)
- Spontaneous secretion, flow of breast milk (galactorrhea)
- Individuals who are biologically female
 - **Irregular menstrual cycles:** sometimes complete lack of menstruation (amenorrhoea); no ovulation → infertility
 - Galactorrhea
 - Painful breasts
- Visual impairment, headaches when pituitary adenoma presses on optic nerve

DIAGNOSIS

DIAGNOSTIC IMAGING

Head MRI/CT scan

- Tumors/lesions in hypothalamic-pituitary area: if none + high serum levels: idiopathic hyperprolactinemia

SIGNS & SYMPTOMS

- Individuals who are biologically male
 - Impaired genital activity (hypogonadism) → infertility, impotence
 - Decreased libido

LAB RESULTS

- High serum prolactin levels

OTHER DIAGNOSTICS

- Lower bone density
- Pregnancy/hypothyroidism

TREATMENT

MEDICATIONS

- **Tumor:** dopamine agonist (inhibit prolactin production, secretion)
 - Bromocriptine/cabergoline

SURGERY

- Surgical removal of tumor
 - High rate recurrence

HYPOPITUITARISM

osms.it/hypopituitarism

PATHOLOGY & CAUSES

- Disorders caused by complete/partial lack of pituitary hormone production, secretion

CAUSES

- Tumors
 - Pituitary adenomas → compression → intracranial pressure → destruction of pituitary
 - Brain (e.g. metastatic cancer)
 - Body
- Traumatic injury, shock, stroke → ischemia
- Vascular
 - Hemorrhages (e.g. aneurysms, subarachnoid hemorrhage)
- Radiation
- Infections
 - Brain (e.g. meningitis)
 - Abnormal brain cells/substance infiltrations (e.g. hemochromatosis)
 - Autoimmune disorders (e.g. autoimmune hypophysitis)
- Congenital (defect in transcription factors)
 - PROP1 gene mutation → hormone deficiency (most common)
 - Pituitary transcription factor 1 (PIT-1) mutation → GH, prolactin, TSH deficiencies
- Hypothalamic dysfunction, decrease in releasing hormones

SIGNS & SYMPTOMS

- Occur when $\geq 75\%$ of anterior pituitary nonfunctional
- Vary depending on hormone affected
- Sequence of loss: "**Go Look For The Adenoma**" (see mnemonic)
- If tumor present
 - Pressure on optic chiasm → visual disturbances
 - Increased intracranial pressure → headache



MNEMONIC: Go Look For The Adenoma

Pituitary adenoma sequence of loss

Growth hormone (GH)

Luteinizing hormone (LH)

Follicle-stimulating hormone (FSH)

Thyroid-stimulating hormone (TSH)

Adrenocorticotrophic hormone (ACTH)

DIAGNOSIS

LAB RESULTS

- Blood tests
 - Serum thyroid levels (T_3/T_4)
 - ACTH secretion (measure serum cortisol in the morning)

TREATMENT

MEDICATIONS

- Hormone replacement
 - ACTH deficiency: hydrocortisone
 - TSH deficiency: levothyroxine

- FSH/LH deficiency: testosterone (for individuals who are biologically male); estrogen-progestin (for premenopausal individuals who are biologically female)

SURGERY

- Surgical excision of tumors

HYPOPROLACTINEMIA

osms.it/hypoprolactinemia

PATHOLOGY & CAUSES

- Low serum prolactin levels due to damaged lactotroph cells in anterior pituitary

CAUSES

- Sheehan's syndrome
 - Postpartum hemorrhage → hypotension, decreased circulation to pituitary, ischemia, damaged lactotroph cells
- Medications
 - Dopamine, dopamine agonists; inhibit prolactin release
- Tumors
 - Pressure on pituitary/hypothalamus → damage lactotroph cells

SIGNS & SYMPTOMS

- Individuals who are biologically female and breastfeeding
 - Decreased lactation (agalactorrhea)

DIAGNOSIS

DIAGNOSTIC IMAGING

MRI

- Tumor confirmation

LAB RESULTS

- Low prolactin levels despite receiving thyrotropin-releasing hormone (TRH)
 - Individuals who are biologically female: < 3µg/L
 - Individuals who are biologically male: < 5µg/L

TREATMENT

MEDICATIONS

- Dopamine antagonists
 - Oppose dopamine in individuals who want to breastfeed

SURGERY

- Surgical removal of tumor

PITUITARY APOPLEXY

osms.it/pituitary-apoplexy

PATHOLOGY & CAUSES

- Pituitary function impaired due to hemorrhage into gland
- Hemorrhage → blood collects within pituitary interstitium → swelling → infarction, loss of pituitary function → compression of surrounding structures

RISK FACTORS

- Intracranial tumors, head trauma, neurosurgery, Sheehan's syndrome (postpartum pituitary necrosis)

COMPLICATIONS

- Hypopituitarism, neuronal damage

SIGNS & SYMPTOMS

- Meningeal stretching
 - Severe headache
- Optic chiasm compression
 - Diplopia, bitemporal hemianopia
- Parenchymal compression
 - Mental status changes
- Clinical manifestations of hypopituitarism (e.g. ↓ ACTH → ↓ cortisol → hypoglycemia, hypotension, adrenal crisis)

DIAGNOSIS

DIAGNOSTIC IMAGING

CT scan/MRI

- Enlarged pituitary gland; hyperintense blood-filled center

LAB RESULTS

- ↓ pituitary hormone levels, target tissue hormones

TREATMENT

MEDICATIONS

- Hormone replacement
 - Glucocorticoids (emergent), levothyroxine

SURGERY

- Surgical decompression
- Transphenoidal resection of pituitary gland

SHEEHAN'S SYNDROME

osms.it/sheehans-syndrome

PATHOLOGY & CAUSES

- AKA postpartum pituitary gland necrosis
- Destruction of lactotroph cells of anterior pituitary in setting of postpartum hemorrhage

CAUSES

- Pituitary increases in size during gestation → metabolic activity of lactotrophs increase, blood supply does not → pituitary vulnerable to perfusion decrease → hypovolemia, hypotension, shock → pituitary infarction, necrosis

SIGNS & SYMPTOMS

- Pituitary dysfunction

DIAGNOSIS

DIAGNOSTIC IMAGING

MRI

- Pituitary ring sign (halo around empty sella)

LAB RESULTS

- Pituitary hormone levels

OTHER DIAGNOSTICS

- Obstetric history

TREATMENT

MEDICATIONS

- Glucocorticoid replacement (emergent) if adrenal insufficiency
- Ongoing hormone replacement as needed

SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION (SIADH)

osms.it/SIADH

PATHOLOGY & CAUSES

- Inappropriate ADH secretion → ↓ water excretion
 - ADH overproduced, secreted → highly concentrated urine, ↓ volume
 - ↑ intake of fluids, ADH secretion → water retention → dilutes plasma sodium levels → hyponatremia

CAUSES

- Central nervous system (CNS) disorders enhance ADH production, release
 - Trauma, stroke, hemorrhage, infection
 - Mental illness, though carbamazepine effects
- Ectopic production of ADH
 - *Lung malignancies*: e.g. small cell carcinoma

- *Nonmalignant lung disorders:* pneumonia, tuberculosis, cystic fibrosis (CF)
- Medications
 - Anticonvulsants, opioids, sulfonylureas
- Injury/surgical removal of pituitary

SIGNS & SYMPTOMS

- Body weakness
 - Fatigue, dizziness, confusion, nausea, lethargy; anorexia
- Muscle cramps
 - Myoclonus, tremors
- Seizures

DIAGNOSIS

LAB RESULTS

- Urinalysis
 - Highly concentrated urine
- Serum tests
 - Hyponatremia, low plasma osmolarity

TREATMENT

MEDICATIONS

- ADH receptor antagonist (e.g. tolvaptan)

OTHER INTERVENTIONS

- Water restriction
 - < 800mL daily
 - If SIADH associated with subarachnoid hemorrhage, fluid restriction not recommended
- IV hypertonic saline administration for severe cases, oral salt tablets, loop diuretics
- Urea administration
 - Increases urine output



NOTES

HYPERTHYROIDISM & HYPOTHYROIDISM

GENERALLY, WHAT ARE THEY?

PATHOLOGY & CAUSES

- Imbalance in thyroid hormones triiodothyronine (T_3), thyroxine (T_4) → alterations in metabolism

CAUSES

Hyperthyroidism

- Thyroid gland hyperfunction → overproduction of thyroid hormones
 - Primary:** dysfunction of thyroid gland
 - Secondary:** ↑ thyroid-stimulating hormone (TSH) secretion by pituitary gland

Hypothyroidism

- Thyroid hormone deficiency
 - Primary:** dysfunction of thyroid gland
 - Central (secondary):** pituitary/hypothalamic gland dysfunction → ↓ thyrotropin-releasing hormone (TRH)/TSH

COMPLICATIONS

- Hyperthyroidism:** thyroid storm
- Hypothyroidism:** myxedema, cretinism (infants, young children)

SIGNS & SYMPTOMS

- Hyperthyroidism:** hypermetabolic state, related to sympathetic nervous system stimulation
- Hypothyroidism:** hypometabolic state

DIAGNOSIS

DIAGNOSTIC IMAGING

Radioiodine uptake scan (RAIU)

- Measures thyroid function
 - Ability to absorb radioactive iodine (^{123}I)

Ultrasound

- Size of thyroid; characteristics of nodules/cysts

Color flow Doppler sonography (CFDS)

- Thyroid blood flow velocity, vascularity

LAB RESULTS

- Serum levels of TSH, total T_4 , free (unbound) T_4 , total T_3 , thyroid-stimulating immunoglobulins (TSI), TSH-receptor antibodies (TRAb)

TREATMENT

MEDICATIONS

Hyperthyroidism

- Antithyroid medication
- Beta blockers for symptomatic thyrotoxicosis

Hypothyroidism

- Exogenous thyroid hormone replacement

SURGERY

- Hyperthyroidism
 - Radioactive thyroid ablation
 - Thyroidectomy

EUTHYROID SICK SYNDROME

osms.it/euthyroid-sick-syndrome

PATHOLOGY & CAUSES

- Older term; describes acquired, transient central hypothyroidism in severely sick
 - Thought to be euthyroid despite $\downarrow T_3$ +/- T_4 concentrations
 - Transient central hypothyroidism coincident with peripheral T_3 metabolism/production abnormalities
- \downarrow 5'-monodeiodinase activity \rightarrow \downarrow peripheral (skeletal muscle, liver, kidney) $T_4 \rightarrow T_3$ conversion \rightarrow $\downarrow T_3$ serum concentration
- \uparrow 5'-monodeiodinase (D3) activity \rightarrow \uparrow conversion of $T_3 \rightarrow rT_3 \rightarrow \downarrow T_3$ serum concentration ($\uparrow rT_3$, T_2 breakdown products)

CAUSES

- Poor caloric intake
- High endogenous serum cortisol in setting of exogenous glucocorticoid therapy
- Circulating inhibitors of deiodinase activity (e.g. free/nonesterified fatty acids)
- Medications (e.g. amiodarone; propranolol, in high doses)
 - Inhibit 5'-monodeiodinase activity
- Cytokines
 - Tumor necrosis factor (TNF), interferon-alpha (IFN- α), nuclear factor kappa-beta (NF- κ B), interleukin 6 (IL-6)
- Impaired peripheral T_4 uptake \rightarrow $\downarrow T_3$ production

RISK FACTORS

- Severe illness, intensive care unit (ICU) hospitalization

COMPLICATIONS

- Myxedema coma

SIGNS & SYMPTOMS

- Similar to hypothyroidism, not attributable to critical illness
 - Fatigue, cold intolerance, weight loss/gain, constipation, muscle cramps, headache, hair loss/brittleness, menstrual irregularities

DIAGNOSIS

LAB RESULTS

- Serum TSH (required for diagnosis)
 - Detects TSH suppression

TREATMENT

OTHER INTERVENTIONS

- Standard replacement therapy (e.g. levothyroxine)
 - No benefit, unless diagnosis of preceding hypothyroidism/progression to myxedema coma

GRAVES' DISEASE

osms.it/graves-disease

PATHOLOGY & CAUSES

- Autoimmune disease; production of antibodies against TSH receptor
- **Most common cause** of hyperthyroidism (80%)
- Thyroid-stimulating immunoglobulin (TSI) antibody **binds to TSH receptors**, acts as analog

RISK FACTORS

- Genetic; polymorphisms in CTLA4, PTPN22, HLA-DR3 allele
- Peak incidence occurs at 20–40 years old
- Individuals who are biologically female affected 10 times more often

COMPLICATIONS

- Congestive heart failure, osteoporosis
- Thyroid storm
- Autoimmune conditions
 - Rheumatoid arthritis, systemic lupus erythematosus, pernicious anemia, diabetes mellitus Type I
- Radioiodine treatment → hypothyroidism

SIGNS & SYMPTOMS

- Effects of TSI
 - Thyroid hypertrophy, hyperplasia → diffuse goiter
 - Increased synthesis, release of T3, T4
 - Follicular cells express molecules on surface, attract nearby T cells → T cells bind to follicular cells, infiltrate interstitium of thyroid tissue
 - TSI stimulation of fibroblasts in eye orbit → **increased production of glycosaminoglycans** → local inflammation, swelling → exophthalmos, lid retraction

- Exophthalmos dries eyes → corneal ulcers; weakens muscles controlling eye, upper lid
- Infiltrative dermopathy
 - Glycosaminoglycan builds up → pretibial myxedema → non-pitting edema
- Pretibial myxedema

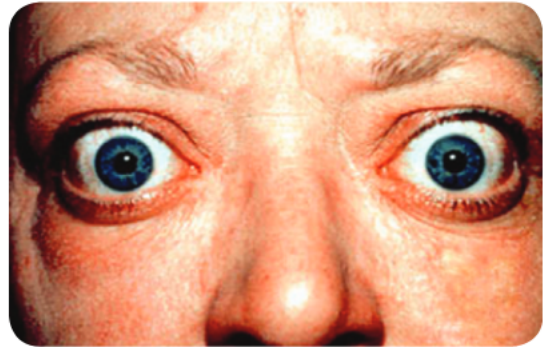


Figure 19.1 The clinical appearance of Graves' disease. There is proptosis and lid retraction bilaterally.

DIAGNOSIS

DIAGNOSTIC IMAGING

- Radioiodine scans, measurements of iodine uptake
 - Diffusely increased

LAB RESULTS

- ↓ TSH, ↑ T3, ↑ T4, ↑ TSI

TREATMENT

MEDICATION

- Antithyroid medication
 - Thioamides
- Beta-blockers

SURGERY

- Thyroidectomy
- Radioiodine radioisotope surgery
 - Partially/completely destroy thyroid gland with radiation

OTHER INTERVENTIONS

- Ophthalmopathy
 - Steroids, radiation and surgery

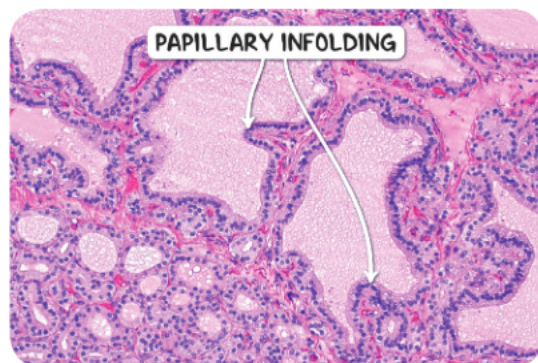


Figure 19.3 The histological appearance of the thyroid gland in Graves' disease. There are enlarged thyroid follicles lined by hyperplastic follicular epithelium. The epithelium demonstrates papillary infolding.

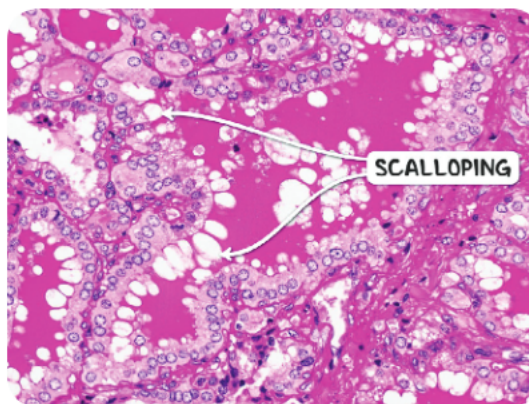


Figure 19.2 The histological appearance of scalloped colloid within a hyperplastic thyroid follicle; a classic sign of Graves' disease.

HYPERTHYROIDISM

osms.it/hyperthyroidism

PATHOLOGY & CAUSES

- Disorder caused by excessive amount of thyroid hormone produced by overactive thyroid gland
- ↑ thyroid hormone synthesis, secretion → thyrotoxicosis (↑ circulating thyroid hormones)

CAUSES

- Autoimmune
 - Graves' disease (most common cause)
- TSH-related disease
 - TSH-secreting pituitary adenoma;

stimulation of TSH receptors due to excess hCG (e.g. trophoblastic tumors, hyperemesis gravidarum)

- Solitary autonomous adenoma
- Excessive iodine ingestion

RISK FACTORS

- More common in individuals who are biologically female
- Smoking, genetic inheritance (Graves' disease)

COMPLICATIONS

- Thyroid storm

SIGNS & SYMPTOMS

- Thyroid
 - Normal/enlarged, with/without palpable nodules (may be diffusely firm, tender)
- Cardiovascular
 - Bounding, rapid pulse; hypertension; palpitations
- Respiratory
 - Tachypnea, dyspnea on exertion
- Gastrointestinal (GI)
 - ↑ appetite/↓ weight; hyperdefecation
- Integumentary
 - Warm, flushed, moist skin; patchy hair loss; thyroid acropachy (digital clubbing); infiltrative dermopathy (pretibial myxedema)
- Musculoskeletal
 - Osteoporosis (↑ bone resorption); skeletal muscle atrophy
- Neurological
 - Heat intolerance, fine tremor, agitation, insomnia
- Reproductive
 - Menstrual irregularities, ↓ libido, infertility
- Ocular changes (Graves' disease)
 - Wide, staring gaze; lid lag, exophthalmos

DIAGNOSIS

DIAGNOSTIC IMAGING

RAIU

- ↑ ^{123}I uptake confirms hyperthyroidism

CFDS

- ↑ blood flow due to thyroid hyperactivity

Ultrasound

- Benign/malignant nodules (e.g. microcalcifications, hypoechogenicity in malignant nodules)

LAB RESULTS

- ↓ TSH, ↑ free T_4 , total/free T_3
 - Confirms hyperthyroidism with suppressed TSH
- ↑ TSH, free T_4 , total/free T_3
 - Confirms TSH-induced hyperthyroidism
- ↑ TRAb/TSI

TREATMENT

MEDICATIONS

- Antithyroid drugs

SURGERY

- Thyroidectomy

OTHER INTERVENTIONS

- Radioactive thyroid ablation

HYPOTHYROIDISM

osms.it/hypothyroidism

PATHOLOGY & CAUSES

- Hypometabolic state caused by underproduction of thyroid hormones T_3 , T_4
- ↓ availability of thyroid hormone → general slowing of thyroid hormone-induced cell metabolism
- Accumulation of matrix glycosaminoglycans in interstitial space → myxedema

TYPES

Primary hypothyroidism (thyroid gland dysfunction)

- Iodine deficiency
- **Autoimmune:** Hashimoto's thyroiditis
 - Autoantibodies against thyroglobulin (Tg), thyroid peroxidase (TPO), TSH receptor → bound antibodies facilitate T-cell, complement-mediated immune destruction of thyroid cells; steric hindrance at TSH receptor
- Congenital
 - Inborn errors of thyroid hormone metabolism
 - Thyroid agenesis/hypoplasia
- Iatrogenic
 - Treatment of hyperthyroidism, thyroid neoplasm (radiation, surgical)
- Medication-induced
 - Overdose of antithyroid drugs (propylthiouracil, methimazole)
 - Agents ↓ T_4 absorption (cholestyramine, iron salts)
 - Agents ↓ T_4 → T_3 conversion (amiodarone)
 - Agents ↓ clearance of T_4 (phenytoin, carbamazepine)
 - **Others:** lithium carbonate, interferon alpha, IL-2, tyrosine kinase inhibitors (esp. sunitinib), P-aminosalicylic acid

Secondary, tertiary hypothyroidism (central hypothyroidism)

- Disorder of pituitary/hypothalamus/ hypothalamic-pituitary communication → ↓ TSH/TRH
 - **Hypopituitarism:** surgical resection/ radiation for adenoma, trauma, postpartum pituitary necrosis (Sheehan's syndrome), infiltrative disease
 - **Hypothalamic damage:** radiation, granulomas, neoplasms

RISK FACTORS

- ↑ age
- More common in individuals who are biologically female

COMPLICATIONS

- Myxedema coma
 - Common in older individuals who are biologically female with longstanding hypothyroidism; precipitated by acute event (e.g. trauma, infection, myocardial infarction)
- Dyslipoproteinemias
- Dilated cardiomyopathy; ↓ thyroid hormone → dysregulation of myocardial enzymes → ↓ myocardial contractility
- Anemia
 - Hypoproliferative (normochromic, normocytic)/pernicious anemia (most common in chronic autoimmune thyroiditis)
- Hyperprolactinemia → galactorrhea
- ↓ clearance of drugs (e.g. antiepileptic, anticoagulant, opioids) in setting of hypothyroidism → ↑ accumulation of drugs → potential drug toxicity
- Congenital hypothyroidism
 - Failure to thrive, intellectual disability

SIGNS & SYMPTOMS

- Fatigue, cold intolerance, constipation, muscle weakness, headache, weight gain, brittle hair/loss of eyebrow hair, menstrual irregularities, goiter (primary hypothyroidism)
- Neurologic manifestations
 - Difficulty concentrating, poor memory, peripheral neuropathy, carpal tunnel syndrome, ↓ deep tendon reflexes
- Myxedema (nonpitting edema)
 - Periorbital edema, tongue enlargement, puffy facies
- Myxedema coma
 - Altered mental status, hypothermia, multi-organ failure, hypotension, bradycardia, hyponatremia, hypoglycemia, hypoventilation

DIAGNOSIS

LAB RESULTS

- Primary hypothyroidism
 - ↑ TSH, ↓ free T_4
- Central hypothyroidism
 - ↓ free T_4 , ↓/↔/↑ TSH
- Autoimmune autoantibody detection (Hashimoto's thyroiditis)
 - ↑ ↑ anti-TPO/Tg/TSH receptor antibodies

OTHER DIAGNOSTICS

- History, physical examination

TREATMENT

MEDICATIONS

- Synthetic T_4 (levothyroxine) replacement therapy



Figure 19.4 Myxedema of the hands in an individual with hypothyroidism.



Figure 19.5 Pretibial myxedema in an individual with hypothyroidism.

THYROID STORM

osms.it/thyroid-storm

PATHOLOGY & CAUSES

- Severe, acute, life-threatening complication of hyperthyroidism

CAUSES

- Abrupt termination of hyperthyroidism therapy
- Complication of hypothyroid treatment
- Diabetic ketoacidosis
- Stressors (surgery, infection, trauma, childbirth)
- Increased sensitivity of tissues to thyroid hormone, catecholamines

COMPLICATIONS

- Myocardial infarction (MI), heart failure; coma, death

SIGNS & SYMPTOMS

- Exaggerated hyperthyroidism symptoms
 - Heat intolerance → fever
 - Hyperactivity, anxiety → agitation, confusion, seizures, coma
 - Tachycardia → cardiac arrhythmias, high-output heart failure

DIAGNOSIS

LAB RESULTS

- ↓ TSH, ↑ T3, ↑ T4

OTHER DIAGNOSTICS

ECG

- Confirmation

TREATMENT

MEDICATION

- Beta blockers
- Thyroid hormones reduction
 - Thioamides, iodine preparations, glucocorticoids, bile acid sequestrants

OTHER INTERVENTIONS

- Plasmapheresis

TOXIC MULTINODULAR GOITER

osms.it/toxic-multinodular-goiter

PATHOLOGY & CAUSES

- Excess thyroid hormone production from multiple autonomous thyroid nodules, without stimulation of TSH
- Second most common cause of hyperthyroidism; AKA Plummer's disease
- Starts as non-toxic multinodular goiter caused by chronic lack of dietary iodine
 - Lack of iodine → low levels of thyroid hormones → anterior pituitary releases TSH → thyroid hypertrophy, hyperplasia → some parts of thyroid gland more responsive to TSH than others → uneven growth → most responsive follicular cells grow quickly, develop into nodule → multiple nodules appear
 - More follicular cells compensate for low thyroid hormone production → euthyroid state
- Non-toxic multinodular goiter becomes toxic when genetic mutation for TSH receptor occurs in one of dividing follicular cells → cell becomes constitutively active without TSH → overstimulation of thyroid to divide, produce thyroid hormone → toxic multinodular goiter

COMPLICATIONS

- Malignancy (rare)

SIGNS & SYMPTOMS

- Increased synthesis, release of T_3 , T_4 → hyperthyroidism
 - Increased basal metabolic rate, catabolism of proteins, carbohydrates, bone resorption
 - Exacerbation of sympathetic nervous system
 - Impairment of reproductive system

- Thyroid hypertrophy, hyperplasia → goiter
 - Difficulty swallowing, airway obstruction
 - Compression of recurrent laryngeal nerve → hoarse voice
 - Superior vena cava syndrome → facial, arm swelling



Figure 19.6 The clinical appearance of a goiter.

DIAGNOSIS

DIAGNOSTIC IMAGING

- Radioiodine scans, measurements of iodine uptake
 - Uneven ("hot" autonomous nodules)

LAB RESULTS

- ↓ TSH, ↑ T_3 , ↑ T_4

TREATMENT

MEDICATION

- Beta blockers
- Antithyroid medication
 - Thioamides
 - If radioiodine therapy, surgery not appropriate

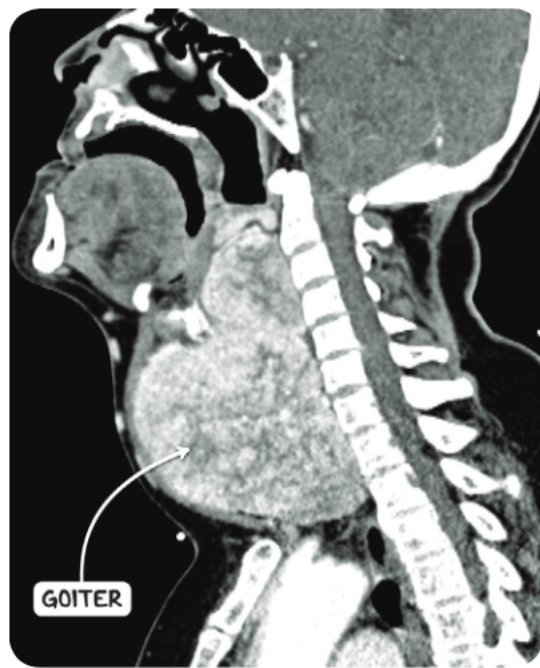


Figure 19.7 A CT scan of the head and neck in the sagittal plane demonstrating a massive goiter extending from the mandible to the suprasternal notch.

SURGERY

- Thyroidectomy
- Radioiodine radioisotope surgery
 - Partially/completely destroy thyroid nodules with radiation

OTHER INTERVENTIONS

- Inject ethanol into nodules



NOTES

NEUROENDOCRINE TUMORS

GENERALLY, WHAT ARE THEY?

PATHOLOGY & CAUSES

- Tumors arising from cells of neuroendocrine origin; most are functional with hormone-secreting capacity
- Can be sporadic; most associated with genetic syndromes

SIGNS & SYMPTOMS

- Mass effect
- Depends on secreted hormone

DIAGNOSIS

DIAGNOSTIC IMAGING

- Location; tumor, lymph node, metastasis (TNM) staging

LAB RESULTS

- Hormone level plasma measurement

OTHER DIAGNOSTICS

- History, physical examination
- Histopathological analysis, tumor grading

TREATMENT

MEDICATIONS

- Chemotherapy; hormonal agonists, antagonists

SURGERY

- Resection

OTHER INTERVENTIONS

- Radiotherapy

CARCINOID SYNDROME

osms.it/carcinoid-syndrome

PATHOLOGY & CAUSES

- Signs, symptoms caused by tumor arising from neuroendocrine cells secreting serotonin
- $\frac{1}{3}$ metastasize, $\frac{1}{3}$ associated with secondary malignancy, $\frac{1}{3}$ multiple tumors
- Most commonly arises from gastrointestinal (GI) tract; followed by lungs, liver, ovaries, thymus
 - Most common small intestine malignancy
 - Appendix most common GI tract site
 - Liver most common site for metastasis; from ileal tumors

SIGNS & SYMPTOMS

- Usually asymptomatic until liver metastasis; symptoms develop occasionally
 - GI tract tumor → hormone secretion → enter into enterohepatic circulation → liver inactivates hormones → no symptoms
 - Liver tumor → hormone secretion → released into circulation + liver dysfunction → symptoms
- Cutaneous flushing
- ↑ intestinal motility, diarrhea
- Collagen fiber thickening, fibrosis
 - Heart valve dysfunction → tricuspid regurgitation, pulmonary stenosis (both right-sided)
- Bronchoconstriction, asthma, wheezing
- Pellagra (niacin/ B_3 deficiency)
 - ↑ serotonin synthesis → ↓ tryptophan → ↓ niacin/ B_3 synthesis
 - Dermatitis, diarrhea, dementia, death

DIAGNOSIS

DIAGNOSTIC IMAGING

CT scan

- Locate tumors

LAB RESULTS

- Niacin deficiency

Urinalysis

- ↑ 5-hydroxyindoleacetic acid

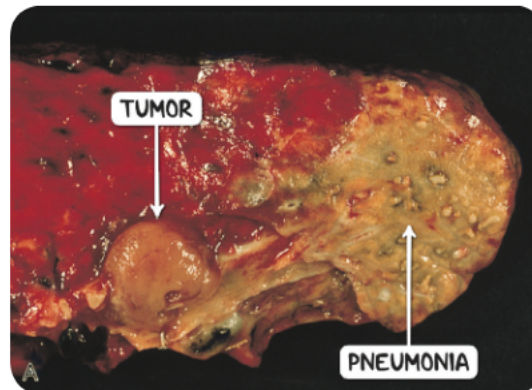


Figure 20.1 The gross pathology a lung carcinoid tumor. The cut surface is firm and yellowish brown. The tumor has obstructed a nearby bronchus, leading to an obstructive pneumonia.

TREATMENT

MEDICATIONS

- Somatostatin analogues
- Niacin supplementation
- Chemotherapy (if malignant)

SURGERY

- Resection

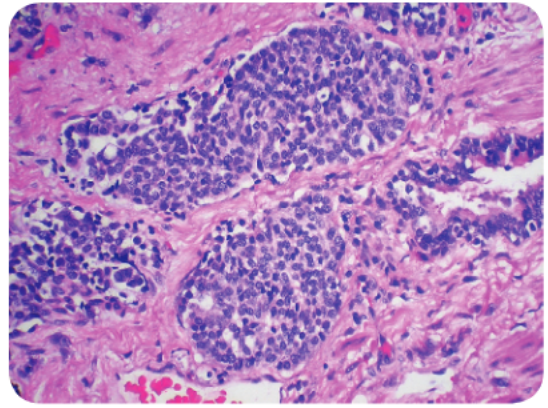


Figure 20.2 The histological appearance of a carcinoid tumorlet. The tumor cells form discrete nests.

MULTIPLE ENDOCRINE NEOPLASIA 1 (MEN1)

osms.it/multiple-endocrine-neoplasia-1

PATHOLOGY & CAUSES

- Autosomal dominant disorder
 - **Characterization:** predisposition for endocrine tumor development
- Tumors may be functional/non-functional (NF); benign/malignant; may affect one/more tissues simultaneously

TYPES

Parathyroid

- Most common

Pancreas, duodenum

- Gastrinoma (ZES), insulinoma, glucagonoma, VIPoma

Anterior pituitary adenoma

- Prolactinoma
- **Other:** corticotroph (ACTH) secreting, thyroid-stimulating hormone (TSH) secreting, growth hormone (GH) secreting, NF

Carcinoid

- Thymic, lung, gastric enterochromaffin-like tumor (NF)

Adrenal cortical tumor

- NF

CAUSES

- Mutation of *MEN1* gene located on chromosome 11 (11q13)
 - Encodes protein *menin* (endocrine organ tumor suppressor)
 - Menin function disruption/inactivation → clonal proliferation → somatic heterozygosity loss of remaining functional allele → endocrine neoplasia formation → primarily affects parathyroid, pituitary, pancreas (3Ps)

RISK FACTORS

- Mutant *MEN1* inheritance

COMPLICATIONS

- **Hyperparathyroidism:** ↓ bone mineral density, nephrolithiasis
- **Pituitary adenoma:** mass effects (e.g. headache, diplopia, visual field defects), Cushing disease, acromegaly
- **Gastrinoma:** peptic ulcer disease, gastrointestinal bleeding
- **Glucagonoma:** necrolytic migratory erythema (NME)
- Metastasis, tumor recurrence

SIGNS & SYMPTOMS

Clinical hormone imbalance, affected organ manifestations

- Hyperparathyroidism
 - Hypercalcemia (e.g. muscle weakness, constipation)
- Pituitary adenoma
 - **Prolactinoma:** menstrual irregularities, galactorrhea, ↓ libido, infertility
 - ↑ **GH:** excessive bone, soft tissue growth; arthralgias
 - ↑ **ACTH:** fat redistribution, plethoric facies, thin skin, striae
 - ↑ **TSH:** hyperthyroidism (e.g. palpitations, tremulousness)
- Pancreatic tumors
 - Glucose dysregulation (insulinomas, glucagonomas); watery diarrhea, hypokalemia, achlorhydria (WDHA) (VIPoma); steatorrhea (somatostatinoma), abdominal pain, gastroesophageal reflux (gastrinoma)
- Carcinoid tumors
 - Dyspnea, wheezing (lung), nausea, vomiting, abdominal pain (gastrointestinal), clinical manifestations of Cushing's syndrome (↑ ACTH from thymic tumor)

Cutaneous manifestations

- Facial angiofibroma, lipoma, collagenoma

DIAGNOSIS

DIAGNOSTIC IMAGING

MRI/CT scan

- Identifies tumor, metastasis, organ structure

changes; TNM staging

Upper GI endoscopy

- Identifies gastric, duodenal carcinoid tumors, peptic ulcers; allows biopsy

Endoscopic ultrasound, somatostatin receptor scintigraphy

- Detects pancreatic neuroendocrine neoplasms (PanNETs)

LAB RESULTS

Blood studies

- Parathyroid tumors
 - ↑ basal serum calcium, ↑ serum PTH, hypercalciuria
- Anterior pituitary adenomas
 - ↑ prolactin, ↑ ACTH, ↑ cortisol, ↑ GH
- PanNETs
 - ↑ fasting gastrin, ↑ insulin, ↑ ↓ glucose, ↑ VIP

OTHER DIAGNOSTICS

- History, physical examination
 - Occurrence of ≥ two primary MEN1 tumor types; identification of first-degree relatives with similar findings
- MEN1 gene-mutation testing

TREATMENT

MEDICATIONS

- Hyperparathyroidism
 - Calcimimetic agents
- Prolactinoma
 - Dopamine agonists
- Gastromas
 - Proton pump inhibitors (PPIs)
- Glucagonomas, insulinomas, somatostatinoma, VIPoma
 - Somatostatin analogue, anti-hyperglycemic agents
- Insulinoma
 - Diazoxide

SURGERY

- Parathyroid tumor
 - Parathyroidectomy, ethanol ablation

- Pituitary adenoma
 - Gamma knife stereotactic radiosurgery, transsphenoidal surgical resection
- Glucagonoma, somatostatinoma, gastrinoma, insulinoma, VIPoma, carcinoid
 - Tumor resection

OTHER INTERVENTIONS

- Correction of fluid, electrolyte, glucose, nutritional abnormalities
- Radiation therapy (e.g. pituitary adenoma)

MULTIPLE ENDOCRINE NEOPLASIA 2 (MEN2)

osms.it/multiple-endocrine-neoplasia-2

PATHOLOGY & CAUSES

- Autosomal dominant disorder
 - **Characterization:** predisposition for medullary thyroid carcinoma (MTC), pheochromocytoma, primary parathyroid hyperplasia

TYPES

MEN 2A

- Most common type, AKA Sipple syndrome
- Variants
 - Classic MEN2A with MTC, pheochromocytoma, primary hyperparathyroidism (milder than MEN1) (MEN2A with cutaneous lichen amyloidosis (CLA); MEN2A with Hirschsprung disease (HD))
 - Familial medullary thyroid carcinoma (FMTC)

MEN 2B

- Variants
 - MTC
 - Pheochromocytoma
 - **Other features:** mucosal neuromas (eyelid, lip, tongue), intestinal ganglioneuromas, marfanoid habitus, medullated corneal nerve fibers

chromosome 10 (10q11.2)

- Encodes transmembrane tyrosine kinase receptor RET protein (integral to intracellular signalling that regulates cellular differentiation, proliferation)
- Mutation → RET activation → disulfide-linked RET dimerization → intracellular substrate phosphorylation → clinical syndromes

RISK FACTORS

- RET mutation presence

COMPLICATIONS

- MTC
 - Hypercalcemia, cardiac arrhythmias, nephrolithiasis
- Parathyroid hyperplasia
 - Hyperparathyroidism, nephrolithiasis, osteoporosis
- Pheochromocytoma
 - Hypertension (therapy-resistant)
- HD
 - Functional bowel obstruction, megacolon, enterocolitis
- Intestinal ganglioneuromas
 - Bowel obstruction
- Metastasis

CAUSES

- Defect in RET proto-oncogene located on

SIGNS & SYMPTOMS

- MTC/FMTC
 - Palpable neck mass, cervical lymphadenopathy, facial flushing (peptide secretion by tumor), diarrhea (gastrointestinal fluid, electrolyte secretion from excess calcitonin); clinical Cushing's syndrome manifestations (ectopic corticotropin (ACTH) production)
- Parathyroid hyperplasia
 - Fatigue, muscle weakness, altered mental status, bone pain (↓ bone density), flank pain (nephrolithiasis), nausea, vomiting, thirst, frequent urination
- Pheochromocytoma
 - Hypertension, paroxysms of palpitations, tachycardia, excessive sweating, facial flushing, tremors, anxiety (↑ catecholamines)
- HD
 - Vomiting, abdominal distension, constipation
- CLA
 - Scaly, papular, pigmented, lesions in either interscapular region/extensor surface extremities
- Intestinal ganglioneuromas
 - Abdominal pain, gaseous distension
- Dysmorphic facies
 - E.g. upper-eyelid margin thickening, eversion; nodules on tongue, vermilion border of lips

DIAGNOSIS

DIAGNOSTIC IMAGING

CT scan/MRI

- Tumor identification, TNM staging

Thyroid, neck ultrasound

- MTC
 - Calcification presence

LAB RESULTS

- MTC
 - ↑ carcinoembryonic antigen (CEA), ↑

serum calcitonin, pentagastrin/calcium stimulation test (↑ serum calcitonin)

- Parathyroid hyperplasia
 - ↑ basal serum calcium, ↑ serum PTH, hypercalciuria
- Pheochromocytoma
 - ↑ plasma fractionated metanephrines, ↑ 24-hour urine metanephrine

OTHER DIAGNOSTICS

- Medical history, family history, physical examination
 - **MEN 2A:** ≥ two characteristic neoplasias in individual/close family members
 - **MEN 2B:** mucosal neuromas of lips, tongue; marfanoid habitus; medullated corneal nerve fibers; gut ganglioneuromatosis; MTC
 - FMTC ≥ four MTC cases in families without pheochromocytoma/hyperparathyroidism
- Fine-needle aspiration (FNA) thyroid biopsy
 - **Histological analysis:** MTC with large, pleomorphic, ↑ C cell number
- Rectal biopsy
 - Absent ganglion cells (HD)
- Ophthalmic slit-lamp examination
 - Detects thickened, medullated corneal nerve fibers
- Genetic RET mutation testing

TREATMENT

MEDICATIONS

- Tyrosine kinase inhibitors
- Post-surgical hormone replacement
- Hyperparathyroidism
 - Bisphosphonates/calcimimetics (cinacalcet)
- Cutaneous lichen amyloidosis
 - Intralesional steroids, antihistamines, ultraviolet light/laser therapy

SURGERY

- Tumor resection (e.g. thyroidectomy, adrenalectomy, partial/cortex-sparing adrenalectomy)
- Lymphadenectomy

- HD
 - Resect affected colon segment

NEUROBLASTOMA

osms.it/neuroblastoma

PATHOLOGY & CAUSES

- Neural crest cell tumor arising in adrenal gland/spinal cord
- Fetal development → oncogene, tumor suppressor gene mutation → adequate cellular differentiation failure → tumor formation
- Most common infant cancer; most occur in age < five; better prognosis
- Releases chemokines (esp. CXCL12) → stimulates cell growth, migration → metastasis
- Half metastasize to bone

TYPES

- Three types: differentiation level

Undifferentiated

- Neural crest cells, AKA small blue round cells; contains nerve fibers, AKA neuropil

Poorly differentiated

- Partially displays characteristics of differentiated, undifferentiated

Differentiated

- Surrounded by myelin, AKA Schwannian stroma; better prognosis

SIGNS & SYMPTOMS

- Related to chemokine release; unspecific
- Fever; weight loss; sweating; fatigue

Mass effect

- Horner syndrome → ptosis, miosis, anhidrosis
- Spinal cord compression syndromes → limb weakness, incontinence

- Abdominal mass

Bone metastasis

- Pain, pathologic fractures
- Skull base fractures → battle, "raccoon eyes" sign
- Myelosuppression → anemia, thrombocytopenia, leukopenia → fatigue, easy bruising, frequent infections

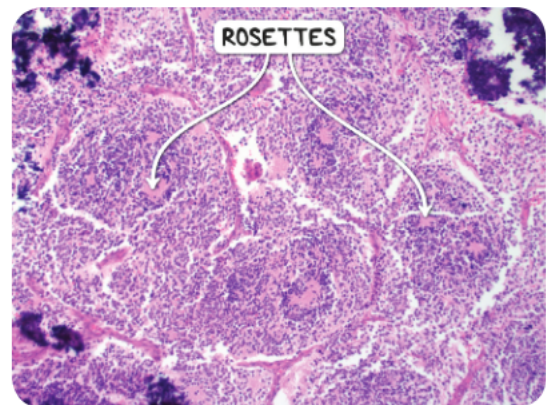


Figure 20.3 The histological appearance of a neuroblastoma demonstrating Homer-Wright rosettes.

DIAGNOSIS

DIAGNOSTIC IMAGING

CT scan

- Renal mass/mass adjacent to spinal nerve roots; confirm diagnosis

LAB RESULTS

- Catecholamine breakdown products: VMA, HMA

Complete blood count (CBC)

- Anemia, leukopenia

TREATMENT

MEDICATIONS

- Metastatic
 - Chemotherapy

SURGERY

- Localized
 - Resection
- Metastatic
 - Resection, bone marrow transplant

PANCREATIC NEUROENDOCRINE NEOPLASMS

osms.it/pancreatic-ne-neoplasms

PATHOLOGY & CAUSES

- AKA PanNETs
 - Functional tumors arising from pancreatic neuroendocrine cells
- Unregulated hormone secretion → effect on target organs → hormone-related clinical syndrome

production by intestinal epithelial cells
→ secretion of fluid, sodium, chloride into intestinal lumen → high-volume secretory diarrhea

TYPES

Insulinoma

- Rare functional tumor
 - Arises from insulin producing pancreatic beta cells
- Most common functioning PanNET
- Usually benign, indolent, small (< 2cm/0.8in), solitary lesions; rarely malignant
- ↑ insulin secretion → hyperinsulinemia → ↓ hepatic gluconeogenesis → hyperinsulinemic hypoglycemia

VIPoma

- Rare functional tumor
 - Arises from pancreatic D-1 cells that produce vasoactive intestinal polypeptide (VIP)
 - AKA Verner–Morrison syndrome/ pancreatic cholera syndrome
- Malignancy: 50%
- ↑ VIP secretion
 - Cellular adenylate cyclase, cAMP

Glucagonoma

- Rare functional tumor
 - Arises from pancreatic glucagon-producing alpha cells
- Usually malignant
- Excessive glucagon
 - ↑ liver's catabolic action → ↑ amino acid oxidation, gluconeogenesis from amino acid substrates → glucagonoma syndrome (amino acid deficiency, ↑ blood glucose, glucose intolerance)
 - Co-secretion of gastrin, VIP, serotonin, calcitonin → diarrhea

Somatostatinoma

- Very rare somatostatin-secreting tumor
 - Arises from pancreatic D-cells
- Commonly located within head of pancreas; may also arise from ampulla, periampullary region of duodenum; rarely in jejunum, liver, colon, rectum
- Usually malignant
 - ↑ somatostatin → digestive organ inhibition → clinical syndrome

RISK FACTORS

Insulinoma

- Multifocal insulinomas associated with MEN 1

VIPoma, glucagonoma

- Associated with MEN 1

Somatostatinoma

- Associated with MEN1, neurofibromatosis type 1 (NF1)

COMPLICATIONS

Insulinoma

- Hypoglycemia, seizures, rarely metastasis

Vipoma

- Dehydration, electrolyte imbalances, metastasis

Glucagonoma

- NME, weight loss (secondary to hyponutrition)
- Diabetes, chronic diarrhea, venous thrombosis (deep vein thrombosis, pulmonary embolism)
- **Neuropsychiatric complications** (e.g. depression, psychosis, agitation, paranoid delusions)
- Metastasis

Somatostatinoma

- Cholelithiasis, diabetes mellitus, metastasis

- ↑ vasodilation → flushing

Glucagonoma

- Hyperglycemia, weight loss
- NME
 - Erythematous, sometimes painful rash with papules/plaques on face, perineum, extremities; hair loss, nail dystrophy
 - *If mucous membranes affected:* glossitis, angular cheilitis, stomatitis, blepharitis

Somatostatinoma

- Classic syndrome
 - ↓ cholecystokinin → coledithiasis
 - ↓ pancreatic enzyme, ↓ intestinal lipid absorption → **steatorrhea**
 - ↓ gastrin → hypochlorhydria
 - ↓ insulin → diabetes mellitus
- Abdominal pain
- Weight loss



MNEMONIC: 6 Ds

Glucagonoma symptoms

Dermatitis
Diabetes
Diarrhea
Deep Venous Thrombosis
Deceased Weight
Depression

SIGNS & SYMPTOMS

Insulinoma

- **Whipple's triad:** hypoglycemia, hypoglycemia signs, intravenous (IV) glucose → symptom resolution
 - **Neuroglycopenic manifestations:** visual disturbances, weakness, confusion
 - **Sympathetic/adrenergic manifestations:** diaphoresis, tremors, palpitations, hunger

VIPoma

- **WDHA;** stools tea-colored, odorless
- ↑ potassium secretion into large bowel → hypokalemia
- ↓ gastric acid secretion → hypochlorhydria
- ↑ glycogenolysis → hyperglycemia
- ↑ bone resorption → hypocalcemia

DIAGNOSIS

DIAGNOSTIC IMAGING

Endoscopic ultrasound

- Insulinoma, VIPoma, glucagonoma, somatostatinoma
 - Detects small tumors, establishes local disease extent, allows for needle biopsy

CT scan/MRI

- Insulinoma, VIPoma, glucagonoma, somatostatinoma
 - Tumor localization, TNM staging

CT scan

- VIPoma
 - Homogeneous, well-circumscribed

lesions; may have cystic regions

- Glucagonoma
 - May appear solid/contain central low-attenuation areas
- Somatostatinoma
 - Isodense; may be cystic

MRI

- VIPoma, glucagonoma, somatostatinoma
 - Low signal intensity on T1-weighted images, high signal intensity on T2-weighted images

GLP-1 scintigraphy

- Insulinoma
 - Identifies insulinoma via radiolabeled GLP-1 receptor imaging

Somatostatin receptor scintigraphy

- VIPoma, glucagonoma, somatostatinoma
 - Detects metastases via radiolabeled form of somatostatin analog octreotide (Indium-111 [111-In] pentetreotide)

Functional PET imaging with 68-Ga DO-TATATE

- Glucagonoma, somatostatinoma
 - Detects small tumors

LAB RESULTS

Insulinoma

- Overnight fasting plasma levels/72 hour fast test (inpatient)
 - ↓↓ glucose, ↑ insulin, ↑ proinsulin, ↑ C-peptide

VIPoma

- *Hormonal assay:* ↑ plasma VIP
- ↓ stool osmotic gap (<50mOsm/kg)

Glucagonoma

- *Hormonal assay:* ↑ plasma glucagon
- ↑ glucose

Somatostatinoma

- *Hormonal assay:* ↑ somatostatin
- ↑ glucose

OTHER DIAGNOSTICS

- Histopathological analysis, grading
 - Determines degree of pleomorphism,

hyperchromasia, mitotic activity

TREATMENT

MEDICATIONS

Insulinoma

- *Diazoxide:* inhibits insulin release, enhances glycogenolysis

VIPoma

- Somatostatin analogue

Glucagonoma, somatostatinoma

- Somatostatin analogue
- Anti-hyperglycemic agents

SURGERY

Insulinoma, VIPoma, glucagonoma, somatostatinoma

- *Resection*
- Ultrasound-guided fine needle ethanol ablation (insulinoma only)

OTHER INTERVENTIONS

Insulinoma

- Oral carbohydrate administration; IV glucose

VIPoma

- *Manage complications:* fluid, electrolyte replacement
- Treat metastatic disease (e.g. chemotherapy, radiation)

Glucagonoma, somatostatinoma

- Correct nutritional deficiencies
- Treat metastatic disease (e.g. chemotherapy, radiation)

PHEOCHROMOCYTOMA

osms.it/pheochromocytoma

PATHOLOGY & CAUSES

- Pheo = dark; chromo = colored; cyto = cell; oma = tumor
- Arises from chromaffin cells in adrenal medulla; secretes catecholamines
- Rule of 10s: 10% bilateral; 10% in children; 10% metastasize; 10% calcify; 10% extra-adrenal
- Most common adult adrenal medulla tumor
- Most common in older biologically-male individuals; may be part of inherited syndrome (25%)
 - MEN 2A, MEN 2B → *RET* proto-oncogene mutation
 - Von-Hippel-Lindau (VHL) → *VHL* gene mutation
 - Neurofibromatosis type 1 (NF1) → *NF1* mutation → impaired neurofibromin function

SIGNS & SYMPTOMS

- Catecholamine excess-related → ↑ epinephrine, norepinephrine, dopamine
- Sweating, anxiety, palpitations, tachycardia, transient, episodic hypertension, headaches
- May be associated with polycythemia



MNEMONIC: Ps Pheochromocytoma symptoms

Perspiration
Palpitation
Pallor
↑ Blood Pressure (BP)
Pain (headache)

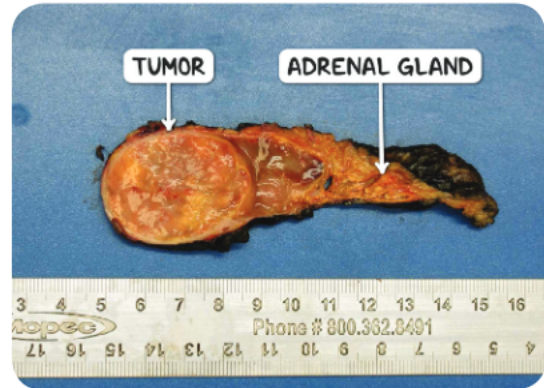


Figure 20.4 The gross pathological appearance of an adrenal pheochromocytoma. The tumor has been bisected revealing a hemorrhagic and necrotic cut surface.

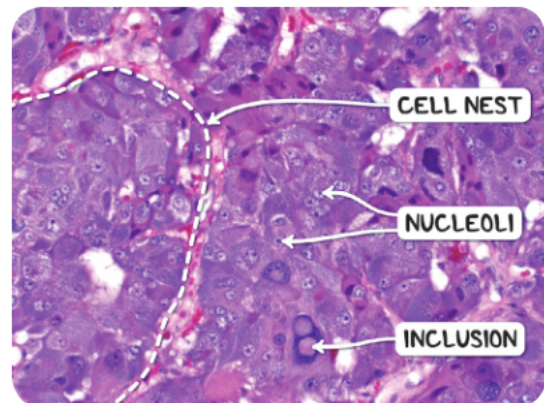


Figure 20.5 The histological appearance of an adrenal pheochromocytoma. The tumor cells are arranged in nests and display prominent nucleoli and occasional nuclear inclusions.

DIAGNOSIS

DIAGNOSTIC IMAGING

CT scan/MRI

- Suprarenal mass; confirm diagnosis

LAB RESULTS

Screening

- Urinary, serum catecholamine breakdown products → homovanillic acid (HMA), vanilmandelic acid (VMA)

CBC

- Polycythemia

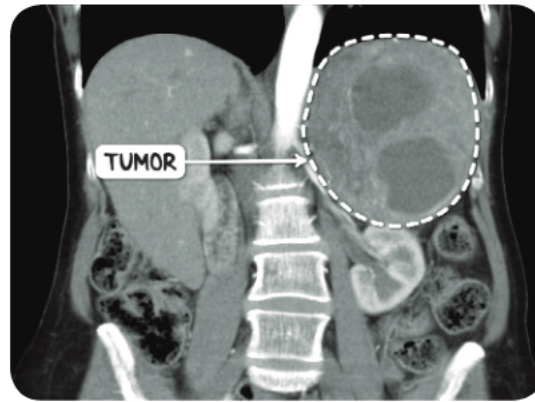


Figure 20.6 An abdominal CT scan in the coronal plane demonstrating a large adrenal pheochromocytoma on the left hand side.

TREATMENT

SURGERY

- Removal (requires pre-operative preparation)
 - Block alpha effects with phenoxybenzamine → give beta blocker

ZOLLINGER–ELLISON SYNDROME (ZES)

osms.it/zollinger-ellison_syndrome

PATHOLOGY & CAUSES

- AKA gastrinoma syndrome
- Functional gastrin-secreting tumor
 - Most commonly arises from “gastrinoma triangle” (head of pancreas, curve of duodenum, cystic, common bile duct)
- Usually malignant
- ↑ gastrin secretion
 - ↑ gastric acid output from parietal cells, enterochromaffin-like (ECL) → malabsorption, mucosal lining erosion (stomach, duodenum)
 - Inhibition of sodium, water absorption by small intestines → loose stools

- May co-occur with other PanNET syndromes

RISK FACTORS

- 20–30% of cases associated with MEN1
- More common in biologically-male individuals

COMPLICATIONS

- Diarrhea, steatorrhea, peptic (potential for bleeding, perforation), esophageal strictures, pancreatitis (with duct obstruction)
- Most gastrinomas malignant

SIGNS & SYMPTOMS

- Abdominal pain; gastroesophageal reflux; nausea, vomiting; dysphagia; weight loss; loose stools; gastrointestinal (GI) bleeding

DIAGNOSIS

DIAGNOSTIC IMAGING

Upper endoscopy

- Enlarged gastric rugal folds, esophagitis, ulcer presence

Endoscopic ultrasound

- Gastrinomas appear as hypoechoic, homogeneous masses

Somatostatin receptor scintigraphy

- Somatostatin analog (111 indium-DTPA-D-Phe1 octreotide) administered, somatostatin analog binds to somatostatin Type II receptors on gastrinomas
- Visualize gastrinoma(s), metastatic lesions

LAB RESULTS

- Basal (fasting) gastrin levels: ↑ serum gastrin

Secretin stimulation test

- Secretin administered IV
- If ZES tumor present
 - ↑ serum gastrin > basal levels
- If other cause of hypergastrinemia
 - Gastrin inhibition

OTHER DIAGNOSTICS

- MEN1 screening

TREATMENT

MEDICATIONS

- Chemotherapy
 - Metastatic disease

SURGERY

- Resection

OTHER INTERVENTIONS

- Proton pump inhibitors
 - ↓ gastric acid
- Somatostatin analog
 - ↓ gastrin levels; may slow tumor growth



NOTES THYROIDITIS

GENERALLY, WHAT IS IT?

PATHOLOGY & CAUSES

- Group of autoimmune disorders resulting in inflammation, destruction, and functional impairment of the thyroid gland

SIGNS & SYMPTOMS

- Hypothyroidism
 - Weight gain despite reduced appetite, constipation
 - Cold intolerance, fatigue, lethargy, weakness
 - Brittle hair and nails, dry skin, hair loss (alopecia)
 - Mental slowness (bradypsychia)
 - Voice hoarseness → compression of recurrent laryngeal nerve
 - Enlarged thyroid gland (goiter)

DIAGNOSIS

- Suspect based on clinical presentation

LAB RESULTS

- Serum antibody levels against thyroid components
- Thyroid biopsy via fine needle aspiration

TREATMENT

MEDICATIONS

- Thyroid hormone replacement → levothyroxine

SURGERY

- Surgical removal if adjacent structures are affected

HASHIMOTO'S THYROIDITIS

osms.it/hashimotos-thyroiditis

PATHOLOGY & CAUSES

- Chronic autoimmune disorder leading to inflammation, gradual destruction and functional impairment of the thyroid gland resulting in hypothyroidism and increased risk of thyroid cancer
- Most common cause of hypothyroidism in areas where dietary iodine is sufficient
- Cause unclear; related to *HLA-DR3* and *HLA-DR5* genes; may occur in combination with Graves' disease; may be influenced by

environmental factors

- Hürthle cells
 - Enlarged follicular cells with an eosinophilic, granular cytoplasm
- Gene mutation → B cell dysfunction → B cell thyroid invasion → B cell germinal centers established within thyroid → B cell activation and autoantibody production → NK cells signaled to destroy thyroid follicular cells + CD4⁺ cells produce inflammatory cytokines + CD8⁺ cells attack thyroid follicular cells → release of stored T₃ and T₄ → transient hyperthyroidism

→ burnout → hypothyroidism → compensatory increase in thyroid-stimulating hormone (TSH), thyrotropin-releasing hormone (TRH)

- Chronic inflammation → connective tissue buildup → enlarged gland
- B cells have the potential to become malignant → **B cell lymphoma** of the thyroid
 - Rare; usually in females over 70 with history of Hashimoto's

SIGNS & SYMPTOMS

Hypothyroidism

- Weight gain despite reduced appetite, constipation
- Brittle hair and nails, dry skin, hair loss (alopecia)
- Cold intolerance, fatigue, lethargy, weakness
- Mental slowness (bradypsychia)
- **Enlarged, nodular thyroid gland** (goiter)
 - Non-tender, firm
 - Voice hoarseness → compression of recurrent laryngeal nerve
 - Stridor → tracheal compression
- Menstrual abnormalities, galactorrhea
- ↑ TRH → ↑ prolactin levels
- Myxedema
 - Nonpitting edema caused by mucopolysaccharide deposition in upper skin layers
 - Most common around tibial area, may also occur around eyes and feet
- Rapidly growing goiter suggests B cell lymphoma of the thyroid

DIAGNOSIS

- Suspect based on clinical presentation

LAB RESULTS

- ↓ T_3 and T_4
- ↑ TSH and TRH
- Autoantibodies against thyroid peroxidase (**anti-TPO**) and against thyroglobulin (**anti-TG**)

- Perform fine needle aspiration (FNA) if B cell lymphoma of the thyroid suspected

TREATMENT

MEDICATION

- Thyroid hormone replacement → levothyroxine

SURGERY

- Goiter affecting adjacent structures → surgical removal

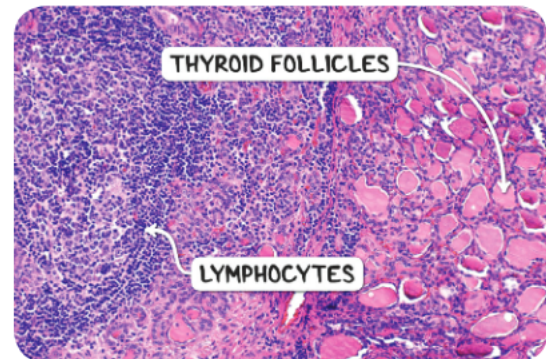


Figure 21.1 The histological appearance of Hashimoto's thyroiditis. The normal thyroid follicles are on the right. The lymphocytic infiltrate has replaced the normal thyroid tissue on the left.



Figure 21.2 A low power image of Hashimoto's thyroiditis, showing the lymphocytic infiltrate forming germinal centres.

POSTPARTUM THYROIDITIS

osms.it/postpartum-thyroiditis

PATHOLOGY & CAUSES

- Autoimmune destruction of the thyroid gland occurring within one year after parturition, resulting in transient thyroid dysfunction and thyroid hormone imbalance
- Related to normal fluctuations in maternal immune function in the setting of subclinical autoimmune thyroid disease
- Autoimmune-related thyroid inflammation (1–4 months postpartum) → damage to thyroid follicles and thyroglobulin → ↑↑ thyroxine (T_4) and triiodothyronine (T_3) release into the blood → hyperthyroidism (last 2–8 weeks)
 - T_4/T_3 stores eventually used up + TSH-induced cessation of new thyroid hormone synthesis → transient hypothyroidism
 - Resolution of inflammation → follicle regeneration → return to normal thyroid levels

RISK FACTORS

- Prior history of postpartum thyroiditis
- Pre-existing hypothyroidism (e.g. Hashimoto's thyroiditis with remaining functional thyroid hormone)
- Type 1 diabetes mellitus
- Familial predisposition (possible inheritance pattern)

COMPLICATIONS

- Chronic hypothyroidism

SIGNS & SYMPTOMS

- Symptoms of hyper- and hypothyroidism are usually mild
- Hyperthyroid phase (↑ metabolic rate)
 - Anxiety
 - Heat intolerance
 - Tachycardia, palpitations
 - Tremor
 - Fatigue
 - Weight loss
 - Diffuse, painless goiter
- Hypothyroid phase (↓ metabolic rate)
 - Impaired concentration
 - Cold intolerance
 - Sluggishness
 - Constipation
 - Dry skin

DIAGNOSIS

DIAGNOSTIC IMAGING

- Radioactive iodine uptake
 - Profoundly suppressed (test is contraindicated if breastfeeding)

LAB RESULTS

- Blood studies
 - Hyperthyroid phase: ↑ T_4 , T_3 ; ↓ TSH
 - Hypothyroid phase: ↓ free T_4 , ↑ TSH
 - ↑ antithyroid peroxidase antibodies
- Thyroid biopsy
 - Lymphocytic thyroiditis - infiltration of lymphocytes, follicular destruction

OTHER DIAGNOSTICS

- History and physical examination

TREATMENT

- Mild symptoms require no treatment

MEDICATIONS

- Symptomatic hyperthyroidism: beta-blocker
- Symptomatic hypothyroidism: levothyroxine

RIEDEL'S THYROIDITIS

osms.it/riedels-thyroiditis

PATHOLOGY & CAUSES

- Rare autoimmune disorder leading to inflammation, fibrotic infiltration, gradual destruction, and functional impairment of the thyroid gland
- May be related to a systemic autoimmune fibrotic disease process
- Component of IgG₄-related disease
 - May also cause fibrosis of salivary glands, kidneys, pancreas and lungs
- IgG₄ attacks thyroid follicular cells → T cells release inflammatory cytokines → abnormal fibroblast activation within thyroid stroma → stromal fibrosis replaces damaged follicles → gland enlarges and hardens → fibrosis spreads to neck structures (parathyroid glands, blood vessels, trachea, muscles, nerves)

SIGNS & SYMPTOMS

- Hardened, wood-like, fixed, painless and enlarged thyroid gland (goiter)
- Hypothyroidism
 - Weight gain despite reduced appetite, constipation
 - Brittle hair and nails, dry skin, hair loss (alopecia)
 - Cold intolerance, fatigue, lethargy, weakness

- Mental slowness (bradypsychia)
- Bradycardia
- Other neck structures affected by compression
 - Tracheal fibrosis → shortness of breath (dyspnea)
 - Recurrent laryngeal nerve fibrosis → voice hoarseness
 - Esophageal fibrosis → dysphagia
 - Parathyroid gland fibrosis → hypocalcemia and tetany (hypoparathyroidism)

DIAGNOSIS

- Suspect based on clinical presentation

LAB RESULTS

- Autoantibodies against thyroid components (anti-TPO)
- ↓ T₃ and T₄
- ↑ TSH and TRH
- Tissue biopsy
 - Predominant fibrous tissue and collagen + lymphocyte infiltration

TREATMENT

MEDICATIONS

- Corticosteroids
- Tamoxifen may decrease goiter size
- Thyroid hormone replacement → levothyroxine

SURGERY

- Debulking or surgical removal if goiter affects adjacent structures