

Hashimoto's Thyroiditis: (chronic lymphocytic)

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→ autoimmune disease leading to gradual failure of thyroid function

→ Age: 45-65 years

→ Sex: More common in women

Etiology: strong genetic predisposition supported by:

[i] concordance of disease in monozygotic twins

[ii] Presence of circulating antithyroid antibodies in asymptomatic siblings of Hashimoto patients

[iii] Association with other autoimmune diseases

→ Associated with polymorphism in genes associated with immune regulation of T-cell responses

• CTLA4 gene

• PTPN22 gene

Pathogenesis: Autoantibodies against $\Rightarrow$ Thyroglobulin & Thyroid peroxidase

Failure of self-tolerance to
thyroid antigens



Induction of thyroid autoimmunity
causing production of circulating
autoantibodies against thyroid antigens



Progressive destruction of
thyrocytes (thyroid epithelial cells)
& replacement of thyroid parenchyma
by mononuclear cell infiltrate &
fibrosis.

Mechanism of thyrocyte death:

① T-cell mediated cell death $\Rightarrow$ $CD8^+$ cytotoxic
T-cells (Type IV hypersensitivity)

② Cytokine mediated cell death $\Rightarrow$ proliferation of
 $CD4^+$ T-cell produces $INF-\gamma$ which activate
macrophages & damage thyrocytes

③ Antibody-dependent cell-mediated cytotoxicity $\Rightarrow$
Antithyroid antibodies bind to antigens on
thyrocytes $\rightarrow$ NK cells induce cell death
(Type II hypersensitivity)

Gross: • diffuse, symmetric enlargement of thyroid • firm, nodular gland
• intact capsule (thyroid is well-demarcated) • cut-surface is pale, gray-tan & shows accentuation of normal lobulation

Microscopy: (Destruction of thyroid parenchyma, Hurthle cell metaplasia, Lymphoplasmacytic infiltrate)

- ① Dense mononuclear inflammatory infiltrate in thyroid parenchyma
- ② lymphoid follicles with well-developed germinal centres
- ③ atrophied thyroid follicles appear smaller than normal
- ④ Hurthle cell metaplasia: metaplastic response of follicular epithelium to injury
→ Hurthle cells (Askanazy / oxyphil cells or oncocytes): abundant eosinophilic, granular cytoplasm, prominent mitochondria (ultrastructurally)
- ⑤ Increased fibrosis (fibrosis does not extend beyond capsule of the gland)

→ FNAC shows Hurthle cells with lymphocytes

Risk in Hashimoto thyroiditis: • other autoimmune diseases
• B-cell non-Hodgkin lymphomas • Papillary carcinomas

Clinical Course: • painless enlargement of thyroid in middle-aged woman
• gradual hypothyroidism • Transient thyrotoxicosis with secondary release of thyroid hormones (Hashitoxicosis)

(3:17)

Graves' Disease: aka Basedow disease $\Rightarrow$ most common cause of hyperthyroidism.

Triad: • Hyperthyroidism • Exophthalmos • Pretibial myxedema

- $\rightarrow$ hyperthyroidism is due to diffuse hyperplasia of thyroid
- $\rightarrow$ exophthalmos is due to infiltrative ophthalmopathy
- $\rightarrow$ pretibial myxedema is due to localised infiltrative dermopathy
- $\rightarrow$ Age: 20-40 years
- $\rightarrow$ Sex: Females $\gg$ Males

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Etiology: strong genetic predisposition supported by:

- [i] concordance of disease in monozygotic twins
 - [ii] Presence of circulating antithyroid antibodies in asymptomatic siblings of Hashimoto patients
 - [iii] Association with other autoimmune diseases
- $\rightarrow$ Associated with polymorphism in genes associated with immune regulation of T-cell responses
- CTLA4 gene
 - PTPN22 gene

Pathogenesis: Autoimmune disease caused by autoantibodies against TSH receptor.
Failure of self-tolerance to thyroid antigens $\rightarrow$ Induction of thyroid autoimmunity causing production of circulating autoantibodies against thyroid antigens

Autoantibodies:

① Thyroid stimulating Ig: IgG which binds to TSH receptor on plasma membrane of thyrocytes

- $\rightarrow$ they act as agonists & stimulate the TSH receptor $\rightarrow$ increased release of thyroid hormones

② Thyroid growth-stimulating Ig: directed against TSH receptor

- $\rightarrow$ causes proliferation of thyroid follicular epithelium $\rightarrow$ diffuse hyperplasia of thyroid gland

③ TSH-binding inhibitor Ig (Anti-TSH receptor Antibody): prevents normal binding of TSH to its receptor

→ Action varies:

- Stimulation: stimulate thyroid epithelial cells → hyperthyroidism
- Inhibition: leading to hypothyroidism
- Coexistence of stimulation & inhibition

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Gross: • symmetrical enlargement of thyroid (due to diffuse hypertrophy & hyperplasia of thyroid follicular epithelium)

- Increased weight of gland
- Cut-section: parenchyma is soft & meaty (like normal muscle)

Microscopy:

Changes in Thyroid:

- ① Epithelial cells lining thyroid follicles are tall & more crowded
- ② Small papillae without fibrovascular core are formed due to crowding of epithelial cells
- ③ Papillae project into lumen of follicle & encroach on the colloid
- ④ Colloid is pale with scalloped margins
- ⑤ Lymphocyte infiltration in interstitium with germinal centres

Changes in Extrathyroidal Tissue:

- Generalised lymphoid hyperplasia
- Myocardial hypertrophy & ischaemia
- Ophthalmopathy
- Dermopathy

Clinical Features:

- ① Thyroid storm ⇒ tachyarrhythmia, hyperpyrexia, shock, coma
- ② Thyrotoxicosis
- ③ Diffuse hyperplasia (enlargement) of thyroid

④ Ophthalmopathy causing exophthalmos (abnormal protrusion of eye ball)

→ wide, staring gaze & lid lag due to sympathetic overactivity

⑤ Infiltrative dermopathy (pretibial myxedema): commonly seen in skin overlying the shin

→ presents as scaly thickening & induration of dermis (due to deposition of GAG's & lymphocytic infiltration)

{ Risks associated with Graves' Disease: • SLE • Pernicious anaemia • Diabetes Type I
• Addison disease

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Laboratory Findings: • Elevated free T_3 & T_4

• Decreased TSH • Increased uptake of radioactive Iodine

[6:54]

(Goiter is the enlargement of thyroid gland without hyperthyroidism)

Diffuse Nontoxic (Simple) Goitre:

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- diffuse enlargement of thyroid without any nodularity
- microscopically consists of large thyroid follicles distended with colloid ($\therefore$ aka colloid goiter)

Types:

Endemic:

- When goiter is present in $>10\%$ population in a given region

Causes:

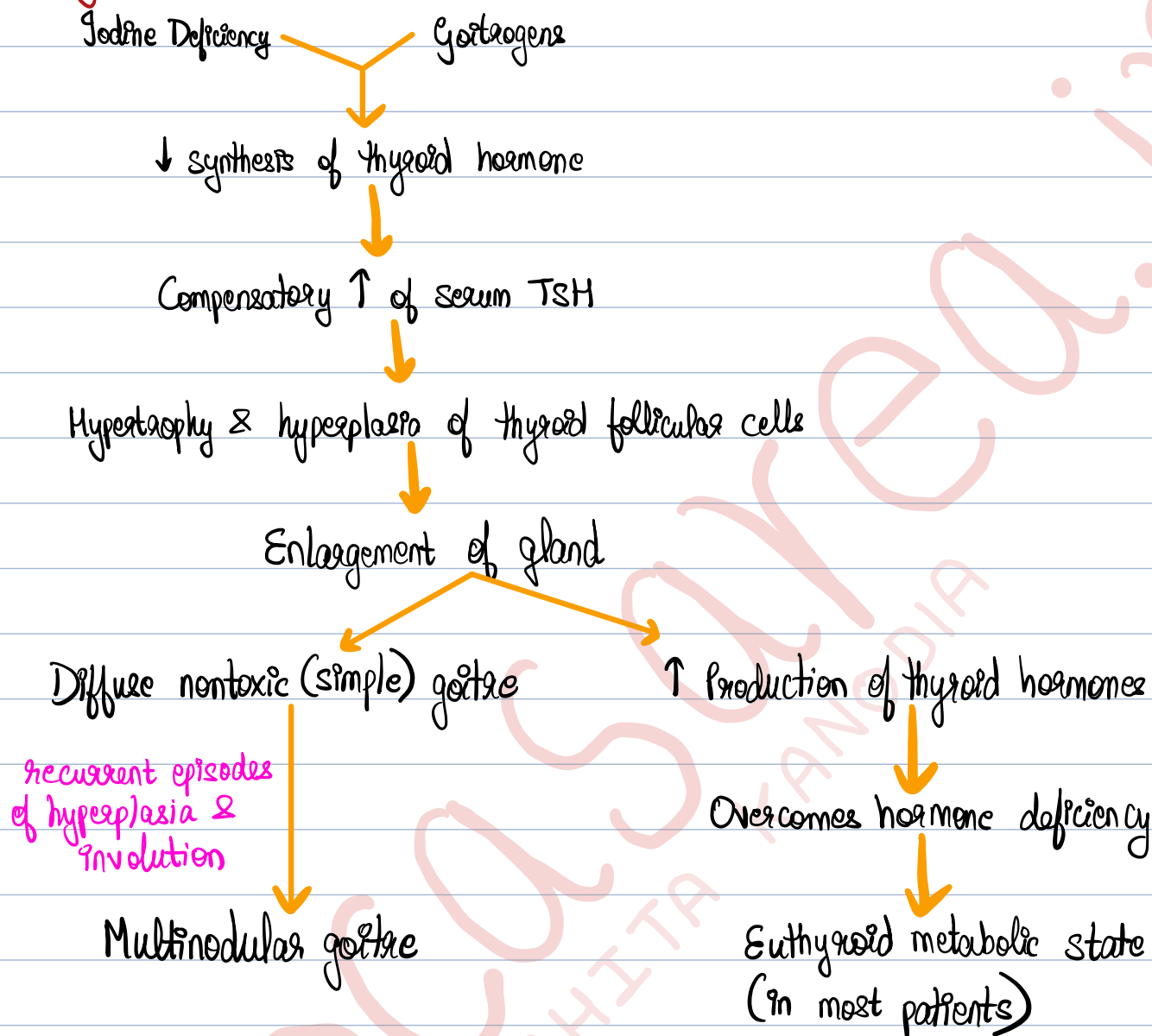
- Iodine deficiency: low iodine in soil, water, food.
 - seen in mountainous area (eg: Himalayas)
 - iodine deficiency $\rightarrow$ decreased synthesis of thyroid hormone $\rightarrow$ compensatory rise in TSH & hyperplasia $\rightarrow$ goiter
- Goitrogens: substance whose ingestion interferes with thyroid hormone synthesis
 - Eg: — Brassicaceae (cruciferaceae) family [cabbage, cauliflower, turnips]
 - Cassava root (contains thiocyanate which inhibits I^- transport in thyroid)

Sporadic: (less frequent)

- Age: Puberty, young adults
- Sex: female preponderance
- Causes:

- Hereditary enzymatic defects (eg: dysmorphogenetic goiter)
- Ingestion of goitrogens
- Unknown cause

Pathogenesis:



Morphology: 2 phases

Hyperplastic phase

Phase of colloid involution

I Hyperplastic Phase:

Gross: moderate, diffuse, symmetrical enlargement of gland

Microscopy: ① Hyperplasia of lining epithelium of thyroid follicles

→ there may be formation of pseudopapillae (Sanderson's Polster) which project into the lumen

② Varying colloid content

II Phase of Colloid Involution: if there is subsequent increase in dietary iodine or if demand for thyroid hormones decreases, there is involution.

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Gross: enlarged thyroid; cut-surface $\Rightarrow$ brown, glassy, translucent

Microscopy: ① flattened follicular epithelial lining

② Abundant colloid

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Clinical Course: (Majority patients are euthyroid)

$\rightarrow$ Mass effects from enlarged gland

Laboratory Findings: • Normal serum T_3 & T_4 • Serum TSH is normal/elevated

Multinodular Goiter (MNG):

→ In long-standing simple goiters, recurrent episodes of hyperplasia & involution produce a more irregular enlargement of thyroid ⇒ MNG

→ Can be sporadic or endemic

Evolution of MNG: → multiple nodules are formed due to variations among follicular cells in their response to external stimuli in long-standing simple goiter

→ Uneven follicular hyperplasia ⇒ some cells proliferate to produce new follicles
⇒ Some follicles show uneven accumulation of colloid

→ Rupture of follicles may produce colloid cysts

→ Rupture of vessels may produce haemorrhages followed by scarring & sometimes, calcification

- Gross:
- ① asymmetric enlargement of thyroid with multiple nodules of varying size
 - ② One lobe of thyroid may be more involved than the other (& may produce pressure on midline structures like trachea & oesophagus)
 - ③ One nodule may become very prominent & appear as a solitary nodule
 - ④ Goiter may grow behind the sternum & clavicles to produce intrathoracic/plunging goiter
 - ⑤ Increased weight of thyroid
 - ⑥ Cut-section: shows multiple irregular nodules containing varying amounts of colloid
↳ Nodules with large amounts of colloid ⇒ glistening & reddish-brown
 - ⑦ Older lesions may show haemorrhage, fibrosis, calcification & cystic change

Microscopy: • multiple nodules of varying shapes & sizes

- Nodules consist of follicles of varying sizes distended with colloid & lined by flat/cuboidal inactive epi.
- Colloid cysts: formed by fusion/rupture of large colloid-filled follicles
- Some nodules show follicular hyperplasia to produce pseudopapillae that project into follicular lumen
- Stroma shows fibrosis & dystrophic calcification (presence of hemosiderin deposits & cholesterol granulomas indicate old haemorrhage)

Clinical Course: (no exophthalmos & pretibial myxedema)

→ usually asymptomatic ; presents as mass in neck

→ large MNG may cause compression of midline structures:

- airway obstruction due to compression of trachea
- dysphagia due to compression of oesophagus
- venous congestion of head & face due to compression of large vessels in neck
- hoarseness of voice due to compression of recurrent laryngeal nerve

→ most patients are euthyroid (normal T_3 , T_4 , TSH)

→ some may develop hyperthyroidism (toxic MNG) $\Rightarrow$ Plummer syndrome

→ Diagnosis: FNAC

Characteristic	Nodule of a Nodular Goiter	Follicular Adenoma
Number of nodules	multiple	single
Encapsulation	poor	good
Structure of follicles within the nodule	variable	uniform
Growth pattern in adjacent gland	comparable growth pattern in adjacent gland	Distinct architecture inside & outside the capsule
Compression of adjacent gland	No compression	Seen outside the capsule

[13:05]

Thyroid Carcinomas:

Major Subtypes:

- (i) Papillary carcinoma
- (ii) Follicular carcinoma
- (iii) Anaplastic (undifferentiated) carcinoma
- (iv) Medullary carcinoma

} follicular cell-derived malignancies

⇒ non-follicular cell-derived cancer

Pathogenesis: ↗ genetic factors
↘ environmental factors

Genetic Factors:

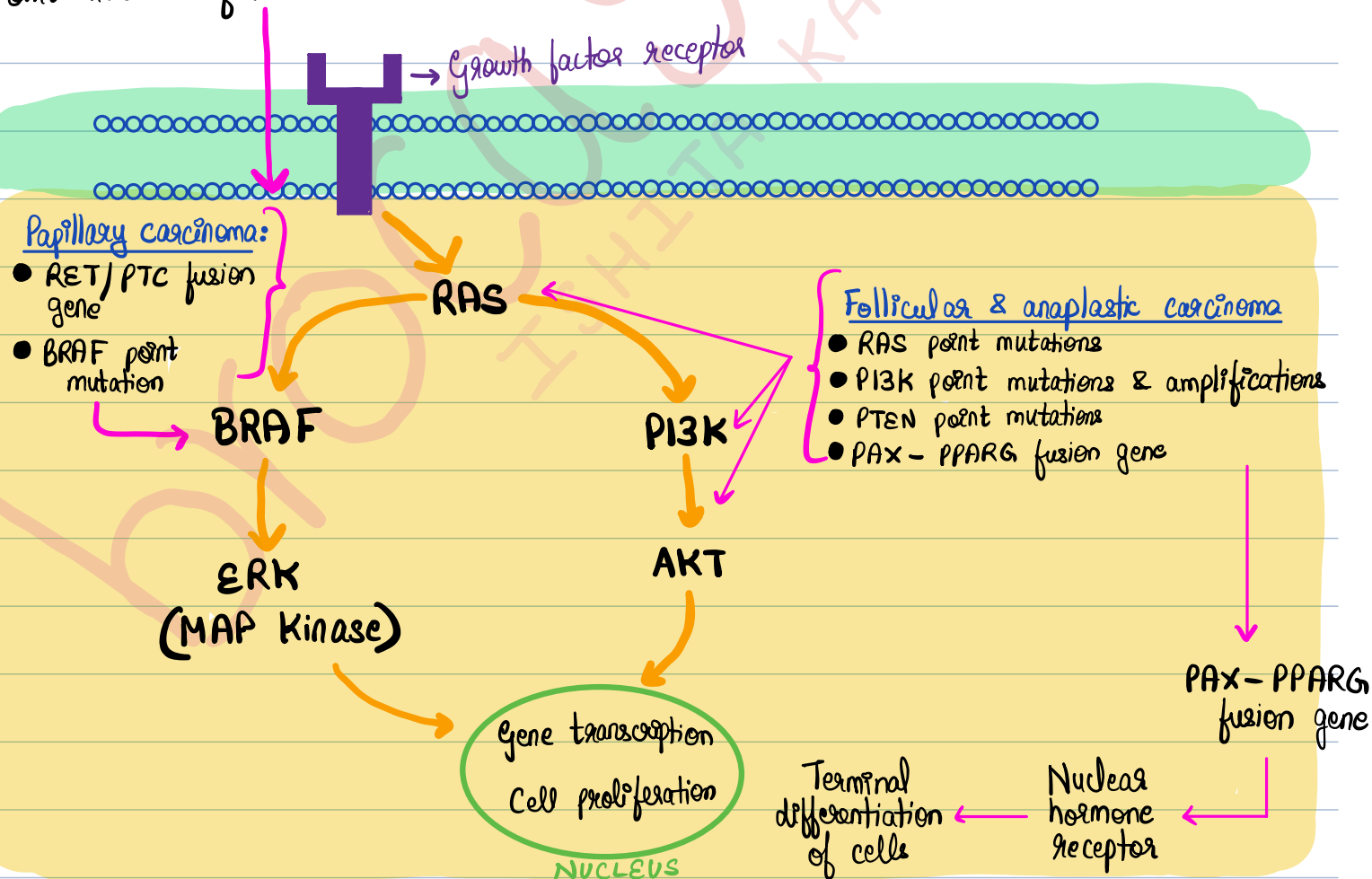
→ Mutations in 2 signalling pathways: (gain-of-function mutation)

- Mitogen associated protein (MAP) Kinase pathway
- Phosphatidylinositol-3-kinase (PI-3K) / AKT pathway

} follicular cell-derived carcinoma

Medullary carcinoma:

- Point mutation of RET



Environmental Factors:

- Ionizing radiations
- Deficiency of dietary iodine

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Papillary Carcinoma of Thyroid:

→ most common thyroid cancer in children

→ most often in women of 30-40 years

→ Age: 25-50

Gross: • solitary or multifocal lesion

- tumours may be well-circumscribed & encapsulated or ill-defined
- Tumour: gray white, firm to hard (may show areas of calcification & fibrosis)
- cut surface may show papillary foci

Microscopy:

- ① complex branching papillae with dense central fibrovascular stalk/core
 - papillae are covered with single - multiple layers of uniform cuboidal - columnar epithelial cells

② Nuclear features:

- Ground glass or Orphan Annie eye nuclei: finely dispersed chromatin $\Rightarrow$ optically clear / empty appearance
- Intranuclear inclusions / intranuclear grooves / pseudoinclusions: invaginations of cytoplasm into nucleus

③ Psammoma Bodies (Calcospherites): concentrically calcified structures present within the papillary core.

④ Spread to regional cervical lymph nodes (vascular invasion is uncommon)

Histological Variants:

(i) Follicular variant (ii) Tall-cell variant (iii) diffuse sclerosing variant (iv) Papillary microcarcinoma

Clinical Course: mostly presents as asymptomatic thyroid nodules / mass in cervical lymph node

→ excellent prognosis

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Medullary Carcinoma of Thyroid: neuroendocrine tumors derived from parafollicular cells or C-cells of thyroid → point mutation in RET gene

→ they secrete calcitonin like normal C-cells

Types: → hypocalcemic hormone

Sporadic: (70%) peak incidence in 40s & 50s

Familial: (30%) with/without association to MEN syndrome 2A or 2B

Gross: → sporadic: solitary nodule; familial: multicentric & bilateral

→ Tumor: firm, pale, gray, infiltrative

→ Larger lesions may show areas of necrosis & haemorrhage & they may extend through the capsule of thyroid

Microscopy:

- ① Tumor cells: polygonal/spindle-shaped cells arranged as nests, trabeculae & even form follicles
- ② Acellular amyloid deposits in the stroma (derived from altered calcitonin polypeptides)
- ③ C-cell hyperplasia: seen in surrounding thyroid of familial medullary cancers (not seen in sporadic lesions)
- ④ Immunohistochemistry: calcitonin can be demonstrated within cytoplasm of tumor cells
- ⑤ Electron microscopy shows membrane-bound electron-dense granules

Clinical Case:

Sporadic Case:

→ Paraneoplastic syndrome in few:

- Diarrhoea due to vasoactive intestinal peptide
- Cushing syndrome due to ACTH

→ presents as mass in the neck

→ Tumor markers: • Calcitonin

- Carcinoembryonic antigen (CEA)

Familial Case:

→ Tumor markers: • Calcitonin • CEA

→ presents with symptoms localised to thyroid

[17:34]

[Neuroblastic tumors: tumors of sympathetic ganglia & adrenal medulla derived from primordial neural crest cells]

Neuroblastoma: most common extracranial childhood solid tumor

→ mostly sporadic ; familial: 1-2%

→ germline mutations in anaplastic lymphoma kinase (ALK) gene in familial neuroblastoma

→ most common malignant tumor of infancy

Gross:

① Site: mostly occur in adrenal medulla

→ other sites: - paravertebral region of abdomen

- posterior mediastinum

- neck & brain

② Size varies from minute nodules to large tumors weighing 1 kg

③ Majority are silent & regress spontaneously

④ May be sharply demarcated by a fibrous pseudocapsule or infiltrate surrounding structures

⑤ Cut-section: soft, gray-tan

Microscopy:

① Tumor cells are arranged in solid sheets

- tumor cells are small, primitive, containing dark nuclei, scant cytoplasm & poorly defined cell borders

② Mitotic activity, karyorrhexis & pleomorphism may be prominent

③ Background shows faintly eosinophilic fibrillary material (neuropil) which represents neuritic processes of primitive neuroblasts

④ Homer-Wright Pseudorosettes: tumor cells concentrically arranged about a central space filled with neuropil.

⑤ Immunohistochemistry: neuron-specific enolase positive

⑥ Electron microscopy: shows small, membrane-bound, catecholamine-containing secretory granules in cytoplasm.

⑦ Maturation: seen in some tumours

↳ characterized by presence of Schwannian stroma (composed of organised fascicles of neuritic processes, mature Schwann cells, fibroblasts)

- Ganglioneuroblastoma: primitive neuroblasts admixed with ganglion cells

- Ganglioneuroma: more mature than ganglioneuroblastoma with larger cells resembling mature ganglion cells

Spread of Tumor: • local infiltration • lymph node spread • blood spread

Clinical Course:

→ children below 2 years of age: present as large abdominal mass, fever, weight loss

→ older children: symptoms of metastases ⇒ bone pain, respiratory symptoms

Laboratory Findings:

→ Raised urine levels of metabolites of catecholamines: • Vanillylmandelic acid (VMA) • Homovanillic acid (HVA)

→ Raised level of blood catecholamines

Prognosis: children < 18 months ⇒ excellent prognosis

→ Amplification of N-MYC oncogene ⇒ high-risk category

Pheochromocytoma: neoplasms composed of chromaffin cells

→ tumor cells synthesize & release catecholamine

Rule of 10's:

→ 10% of pheochromocytoma are extra-adrenal (paragangliomas) ⇒ occur in organs of Zuckerkandl & carotid body

→ 10% of sporadic adrenal pheochromocytomas are bilateral

→ 10% of adrenal pheochromocytomas metastasize & are malignant

→ 10% of adrenal pheochromocytomas are not associated with hypertension

Etiology: germline mutation in one of the genes RET, NF1, VHL & succinate dehydrogenase complex subunit genes - SDHB, SDHC, SDHD.

Gross: • variable size

- Weight: 1 - 4000g (avg. = 100g)
- Large tumors are well-demarcated & may produce a lobular pattern
- Cut surface: yellow tan (small), show necrosis / haemorrhage (large)
- When fresh tumor tissue is incubated in potassium dichromate solution, tumor turns dark brown in colour (due to oxidation of stored catecholamines)

⇒ Chromaffin reaction

Microscopy:

- Zellballen pattern: polygonal to spindle-shaped chromaffin cells or chief cells clustered with sustentacular cells into small nests or alveoli (zellballen) separated by a rich vascular network
- fine granular appearance of cytoplasm due to presence of catecholamine granules (best demonstrated with silver stains)
- round / oval nuclei with stippled salt-&-pepper chromatin
- Electron microscopy shows membrane-bound, electron dense secretory granules
- Neuroendocrine markers (chromogranin & synaptophysin are positive in chief cells)

Spread: definitive diagnosis of malignancy in pheochromocytoma ⇒ metastases

Clinical Course:

① Hypertension in 90% cases: paroxysmal episodes $\Rightarrow$ abrupt precipitous elevation in BP with tachycardia, palpitations, headache, sweating, tremor

$\rightarrow$ induced by sudden release of catecholamines

Complications: catecholamine cardiomyopathy, ventricular arrhythmias

Laboratory Diagnosis: increased urinary excretion of free catecholamines & their metabolites.

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Multiple Endocrine Neoplasia (MEN): (rare autosomal dominant syndrome)

- characterized by hyperplasia & formation of adenomas or malignant tumours in multiple glands.
- MEN syndrome should be considered in all patients with 2 or more endocrine tumours & in patients with solitary tumours who report other endocrine tumours in their family.
- Inactivating mutations in MEN1 (a tumor suppressor gene) on chromosome 11 causes MEN1 syndrome
- MEN2a & 2b are caused by gain of function mutations in RET proto-oncogene on chr. 10
 - constitutive activation of membrane-associated tyrosine kinase RET which controls the development of cells that migrate from the neural crest
- [Loss of function mutation of RET kinase causes Hirschsprung's Disease]
- MEN 4 (rare) is associated with loss-of-function mutations in CDKN1B gene on chr. 12 (which codes for protein p27 which has tumor suppressor activity)

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MEN1 (Weerner's Syndrome):

- Pituitary hyperparathyroidism
- Pituitary tumours
- Pancreatic neuro-endocrine tumours (eg: non-function insulinoma, gastrinoma)
- Bronchial & thymic carcinoids
- Adrenal tumours
- Cutaneous lesions (eg: lipomas, collagenomas, angiofibromas)

ABC - P³

MEN2 (aka MEN 2a / Sipple's Syndrome):

- Primary hyperparathyroidism
- Medullary carcinoma of thyroid
- Pheochromocytoma

P²M

MEN 3 (aka MEN 2b):

- Medullary carcinoma of thyroid (occurs earlier, even within first year of life)
- Marfanoid habitus
- Skeletal abnormalities (eg: craniosynostosis)
- Abnormal dental enamel
- Multiple mucosal neuromas

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SAM³

MEN 4:

- Primary hyperparathyroidism
- Pituitary tumours
- Possible tumours in adrenals, reproductive organs, kidneys
- Possible pancreatic, gastric, bronchial & cervical neuro-endocrine tumours

P⁴

Thyrotoxicosis: systemic syndrome (with hypermetabolic state) caused by exposure to excessive levels of thyroid hormone (free T_3 & T_4)

Causes:

I Associated with hyperthyroidism:

- ① Primary hyperthyroidism:
- Grave's disease
 - Toxic multinodular goiter
 - Toxic adenoma

- ② Secondary hyperthyroidism: — TSH secreting pituitary adenoma

II Not associated with hyperthyroidism:

- Granulomatous thyroiditis
- Struma ovarii
- Factitious thyrotoxicosis

GFs

Causes of hyperthyroidism:

- ① Primary hyperthyroidism: — abnormal thyroid stimulation (Grave's disease)
- intrinsic disease of thyroid gland (Toxic MNG)

- ② Secondary hyperthyroidism: — TSH secreting pituitary adenoma

Clinical Manifestations:

- ↑ BMR
- soft, warm, moist skin
- Heat tolerance
- Sweating
- ↑ cardiac output
- tachycardia
- palpitation
- arrhythmia
- cardiomegaly
- fine tremor
- hyperactivity
- anxiety
- insomnia
- lid retraction → staring appearance
- ↑ stool frequency, diarrhoea
- osteopenia
- thyroid storm

Laboratory findings: • ↓ serum TSH • ↑ free T_4

Pituitary Adenomas:

I Functional:

- a) Lactotroph adenomas: secrete prolactin
- b) Somatotroph adenomas: secrete growth hormone
- c) Corticotroph adenomas: secrete ACTH

II Non-functional: produce only mass effects , silent tumors

Cushing's Syndrome (Hypercortisolism):

Causes:

- Exogenous Causes: administration of exogenous glucocorticoids (in allergic & autoimmune diseases)
- Endogenous Causes:

— ACTH dependent:

- * Primary hypersecretion of ACTH by pituitary disease (Cushing's disease)
- * Secretion of ectopic ACTH by nonpituitary neoplasms

— ACTH independent: Primary adrenocortical neoplasms

Morphology:

- Pituitary: Crooke hyaline change $\Rightarrow$ homogenous & pale appearance of cytoplasm of ACTH-producing cells in anterior pituitary
- Adrenals: One of the following changes is seen:
 - $\Rightarrow$ Cortical atrophy $\Rightarrow$ macronodular/micronodular hyperplasia
 - $\Rightarrow$ diffuse hyperplasia $\Rightarrow$ functional adenoma/carcinoma of adrenal cortex.

Clinical Course:

- weight gain (due to hyperinsulinism from hyperglycemia)
- glucosuria
- polydipsia
- truncal obesity
- moon faces
- buffalo hump
- hypertension
- muscle weakness
- decreased muscle mass
- purple abdominal striae
- osteoporosis
- increased risk of infections

Laboratory findings:

- Primary hypercortisolism — low serum ACTH
- Secondary hypercortisolism — high serum ACTH
- $\uparrow$ urinary free cortisol
- $\uparrow$ serum cortisol

Zollinger-Ellison Syndrome:

Triad: • Hypergastrinemia

- Increased acid production
- Severe peptic ulcer disease

Hypergastrinemia: gastrinomas in small intestine/pancreas → ↑ gastrin secretion → ↑ acid & pepsin secretion.

(Fasting serum gastrin > 1000 pg/mL)

Increased acid secretion: → inactivation of pancreatic enzymes & bile salts → malabsorption & diarrhoea

(↑ number of parietal cells in stomach)

Peptic Ulcers: multiple & recurrent.

Diabetes Mellitus: group of metabolic disorders having features of hyperglycemia

Normal fasting blood glucose: 70-120 mg/dL

	Euglycemic	Prediabetes	Diabetes
Fasting glucose	< 100 mg/dL	100 - 126 mg/dL	> 126 mg/dL
OGTT	< 140 mg/dL	140 - 200 mg/dL	> 200 mg/dL
HbA _{1c}	< 5.7 %	5.7 - 6.4 %	> 6.5 %

(Prediabetes $\Rightarrow$ impaired glucose tolerance)

Classification:

- Type 1 Diabetes: Juvenile-onset DM / Insulin-Dependent DM (IDDM)
- Type 2 Diabetes: Maturity-onset DM / Non-Insulin-Dependent DM (NIDDM)
- Genetic defects of β -cell function: - Maturity-onset diabetes of young (MODY)
 - neonatal diabetes
- Genetic defects in insulin action
- Exocrine pancreatic defects: - chronic pancreatitis - haematochromatosis
- Endocrinopathies: - Acromegaly - Cushing syndrome - hyperthyroidism
 - pheochromocytoma
- Infections: - Cytomegalovirus - coxsackie B virus
- Drugs: - glucocorticoids - thyroid hormone
- Genetic syndrome: - Down syndrome - Klinefelter syndrome - Turner syndrome
- Gestational diabetes mellitus.

Cause: • Autoimmune disease - pancreatic β -cell destruction

- Absolute insulin deficiency

- Idiopathic

Pathogenesis of Type 1 DM:

- Genetic Factors: increased incidence in twins of affected individuals (monozygotic > dizygotic twins)

- HLA-DR3, HLA-DR4 or both

- polymorphism in gene coding insulin, CTLA4 & PTPN22 genes, CD25

- Environmental factors:

- Viral infections: may trigger islet cell destruction (mumps, rubella, coxsackie B, cytomegalovirus)

- Mechanism:

- * Release of hidden or sequestered antigens: activates auto-reactive T-cells

- * Molecular mimicry: viruses produce proteins that mimic β -cell antigens

- * Sharing of antigen epitopes: first infection (predisposing virus) during early life might persist in β -cells; subsequent re-infection with a related virus (precipitating virus) that shares antigenic epitopes may lead to an immune response against β -cells.

Mechanism of β -cell Destruction: autoimmune damage starts many years before the disease becomes clinically evident (hyperglycemia & ketosis occur after >90% of the β -cells have been destroyed)

① Failure of self-tolerance in T-cells: basic abnormality in Type 1 DM

- failure of self tolerance may be due to: - defective clonal deletion of self-reactive T-cells in thymus

- defects in functions of regulatory T-cells

- resistance of effector T-cells to suppression by regulatory cells

② Through cytokines: T_H1 cells may destroy β -cells by secreting cytokines including IFN- γ & TNF.

③ Directly by cytotoxic T-cells: CD8+ CTLs may directly kill β -cells

④ Autoantibodies against β -cell antigens (eg: islet antigens β -cell enzymes): anti-insulin, anti-GAD, anti-ICA512

Pathogenesis of Type 2 DM: multifactorial disease

- Environmental factors: • sedentary lifestyle • dietary habits • obesity
- Genetic factors: • monozygotic twins > dizygotic twins • lifetime risk in an offspring if both parents are affected
- diabetogenic genes present (no evidence of autoimmune basis)

Metabolic Defects in Type II DM: • Insulin resistance • β -cell dysfunction

- Insulin Resistance: decrease / failure of target (peripheral) tissues to insulin action

- Insulin resistance is found even in simple obesity but without hyperglycemia; risk for diabetes increases as BMI increases
- distribution of body fat has an effect on insulin sensitivity $\Rightarrow$ central obesity (abdominal fat) is more associated with insulin resistance than peripheral (gluteal/subcutaneous) fat.
- Causes of insulin resistance in obesity: • nonesterified free fatty acids • adipokines • chronic inflammation in adipose tissue • activation of PPAR γ .

(i) Excess of Free Fatty Acids (FFAs): inverse relation between fasting plasma FFAs & insulin sensitivity

- excess circulating FFAs $\rightarrow$ deposited as triglycerides in liver & muscle $\rightarrow$ $\uparrow$ level of intracellular triglycerides
- excess intracellular FFAs $\rightarrow$ $\uparrow$ fatty acid oxidation $\rightarrow$ accumulation of cytoplasmic toxic intermediates such as diacylglycerol (DAG) & ceramide $\rightarrow$ $\downarrow$ insulin signalling $\rightarrow$ $\uparrow$ gluconeogenesis (insulin normally inhibits hepatic gluconeogenesis)

(ii) Adipokines: adipose tissue acts as a functional endocrine organ & secretes variety of proteins into systemic circulation called adipokines

- Prohyperglycemic adipokines: resistin, retinol binding protein (RBP4)
- Antihyperglycemic adipokines: leptin, adiponectin

(iii) Inflammation: excess FFAs & glucose $\rightarrow$ release of proinflammatory cytokines $\rightarrow$ $\uparrow$ insulin resistance & β -cell dysfunction

- excess FFAs within macrophages & β -cells $\rightarrow$ activation of inflammasome $\rightarrow$ release of cytokine IL-1 β $\rightarrow$ secretion of additional proinflammatory cytokines $\rightarrow$ $\uparrow$ insulin resistance

• β -cell Dysfunction: inadequate insulin secretion by pancreatic β -cells (relative insulin deficiency)

- pancreatic β -cells initially respond to long-term demands of peripheral insulin resistance by undergoing compensatory β -cell hyperplasia leading to hypersecretion of insulin
- at some point, β -cells exhaust their capacity to adapt & normal blood sugar cannot be maintained
∴ impaired glucose tolerance ⇒ Early Stage of β -cell Failure.
- Insulin secretion decreases leading to hyperglycemia ∴ diabetes develops ⇒ Late Stage of β -cell Failure.
- Molecular Mechanisms of β -cell dysfunction:
 - Excess FFAs & decreased insulin signalling (lipotoxicity)
 - Chronic hyperglycemia (glucotoxicity)
 - abnormal incretin effect ⇒ ↓ secretion of hormones that increase insulin release (GIP, GLP-1)
 - direct toxicity by amyloid deposits in islets

Pathogenesis of Complications of Diabetes:

- glycemic control is assessed by estimation of glycosylated hemoglobin Hb_{A1c}
- chronic hyperglycemia → secondary multiple organ damage (kidneys, eyes, nerves, blood vessels)

Formation of Advanced Glycation End-products (AGEs): nonenzymatic glycosylation of proteins

→ Glucose + proteins $\xrightarrow{\text{nonenzymatic glycosylation}}$ Schiff bases (labile) $\xrightarrow{\hspace{1cm}}$ AGEs (stable)

DIRECT ACTION

Cross-linking with extracellular matrix proteins

With Collagen type I
in large vessels

↓ elasticity

Endothelial injury

with Collagen type IV
in basement membrane

↑ extravasation of
fluid

AGE-modified
basement membrane

+
Trapped
LDL

↑ Atherogenesis

Binding to RAGE Receptor

- ↑ releases of proinflammatory cytokines
- ↑ production of reactive oxygen species
- ↑ procoagulant activity

• ↑ proliferation of vascular
smooth muscle

+
Plasma
protein

Basement membrane
thickening

• ↑ cells & synthesis of
ECM

Activation of Protein Kinase C (PKC): intracellular hyperglycemia stimulates synthesis of diacylglycerol (DAG) from glycolytic intermediates → DAG activates intracellular PKC → consequences:

- production of proangiogenic molecules like vascular endothelial growth factor (VEGF) → neovascularization characteristic of diabetic retinopathy
- production of profibrogenic factors (eg: TGF- β) → increased production of ECM & basement membrane material
- production of plasminogen activator inhibitor (PAI-1) → reduces fibrinolysis & favours vascular occlusion (due to atherosclerotic plaque/thrombus formation)

Disturbance in Polyol Pathways: (some tissues do not require insulin for glucose transport eg: nerves, lenses, kidneys, blood vessels)

→ persistent hyperglycemia → ↑ intracellular glucose in these tissues → glucose metabolism by aldose reductase to sorbitol → converted to fructose

↳ utilizes NADPH as a cofactor → NADPH is also needed for regeneration of reduced glutathione (GSH) which protects against injury by free radicals → decrease in GSH → increased cell susceptibility to oxidative stress

Morphology:

Pancreas: lesions of pancreas are not diagnostic

- Reduced number & size of islets
- Infiltration of islets (insulitis) mainly by T-lymphocytes (predominant in type 1 DM)
- amyloid deposition within islets
- increase in the number & size of islets may be seen in nondiabetic newborns of diabetic mothers as a hyperplastic response to maternal hyperglycemia

Blood vessels:

- Hyaline arteriosclerosis: related to the duration of diabetes & level of BP
 - characterized by amorphous, hyaline thickening of wall of arterioles which may narrow the lumen of vessels

→ Diabetic microangiopathy: diffuse thickening of basement membrane (mostly seen in capillaries of skin, skeletal muscle, retina, renal glomeruli, renal medulla)

- capillaries become leakier to plasma proteins than normal
- microangiopathy results in diabetic nephropathy, retinopathy, neuropathy

Clinical Features: Classical Triad • Polydipsia • Polyphagia • Polyuria

Type 1 DM: → Classical triad + ketoacidosis (in severe cases)

→ in the initial 1 or 2 years, exogenous insulin requirement may be minimal; later, its requirement suddenly increases

Consequences of insulin deficiency: (catabolism)

① Carbohydrate metabolism:

- diminished glucose transport into muscle cells & adipose tissue
- reduction of stored glycogen in liver & muscle due to glycogenolysis → further aggravates hyperglycemia
- when hyperglycemia exceeds renal threshold level → glycosuria → osmotic diuresis → polyuria
- water loss through urine + hyperosmolarity due to hypoglycemia → depletion of intracellular water → stimulates osmoreceptors of thirst centers of brain → polydipsia

② Protein & fat Metabolism: catabolism of proteins & fats → negative energy balance → polyphagia

- catabolic effects of insulin cause a paradoxical loss of weight & muscle weakness

③ Diabetic ketoacidosis:

- Diuresis & dehydration: masked insulin deficiency + epinephrine release → ↑ secretion of glucagon → decreased peripheral utilization of glucose + ↑ gluconeogenesis → severe hyperglycemia (500-700 mg/dL) → osmotic diuresis & dehydration

- Activation of ketogenic machinery: insulin deficiency → stimulates lipoprotein lipase → breaks down fat stores → ↑ FFAs → FFAs are esterified to fatty acyl coenzyme A in liver → in mitochondria of liver cells, fatty acyl coA is oxidized to ketone bodies (acetoacetic acid & β -hydroxybutyric acid)

- when rate of production of ketone bodies exceeds the rate of utilization by peripheral tissues → ketonemia, ketonuria
- if excretion of ketone bodies in urine is compromised by dehydration → systemic metabolic ketoacidosis

Type 2 DM: usually occurs above 40 years & frequently in obese individuals

→ Presentation: polyuria, polydipsia, unexplained weakness / weight loss (ketoacidosis is infrequent)

	Type 1 DM	Type 2 DM
Age of onset	Childhood & adolescence	Adult (also seen in childhood)
Weight	Normal / weight loss	Majority are obese
Insulin levels	Progressive decrease	Increased (early); decrease (late)
Circulating islet autoantibodies	Detected (anti-insulin, anti-GAD, anti-ICA512)	Not found
Diabetic Ketoacidosis	Develops in absence of insulin therapy	Nonketotic hyperosmolar coma
HLA association	Major linkage to MHC class I & II genes HLA-DR3 & DR4	No HLA association
Non-HLA genes	Polymorphisms in CTLA4 & PTPN22	Diabetogenic & obesity-related genes
Mode of development	Autoimmune	Multifactorial
Mechanism	Breakdown in self-tolerance to islet autoantigens	Insulin resistance in peripheral tissues, β -cell dysfunction
Insulinitis	Inflammatory infiltrate of T-cells & macrophages in islets	No insulinitis; amyloid deposition in islets
β -cell depletion	Moderate to severe	Mild

Complications: long-term complications of diabetes usually develop 15-20 years after onset of hyperglycemia

Diabetic Macrovascular Disease: lesions of large & medium-sized muscular arteries

- **Atherosclerosis:** increased levels of PAI-1 in diabetics inhibits fibrinolysis & favors formation of atherosclerotic plaques
- **Myocardial infarction:** due to atherosclerosis of coronary arteries
- **Gangrene of lower extremities**
- **Renal vascular insufficiency**
- **Cerebrovascular accidents (stroke)**

Microvascular Disease (Microangiopathy): involves small vessels, capillary dysfunction in target organs

- **Diabetic nephropathy:** leading cause of end-stage renal disease; different stages:
 - (i) Microalbuminuria $\Rightarrow$ earliest manifestation (Urine albumin: 30-300 mg/day)
 - (ii) Nephropathy with macroalbuminuria (Urine albumin > 300 mg/day)
 - (iii) End-stage renal disease
- **Diabetic retinopathy:** lesion $\Rightarrow$ neovascularization caused by hypoxia-induced overexpression of VEGF in retina
 - $\rightarrow$ increased risk for glaucoma & cataract formation
- **Diabetic neuropathy:** involving central & peripheral nervous system
 - $\rightarrow$ Distal symmetric polyneuropathy $\Rightarrow$ affects both motor & sensory function of lower extremities; later may involve the upper extremities leading to "glove & stocking" pattern
 - $\rightarrow$ Autonomic neuropathy $\Rightarrow$ produces disturbances in bowel & bladder function & sometimes, sexual impotence
 - $\rightarrow$ Diabetic mononeuropathy $\Rightarrow$ manifests as sudden footdrop, wristdrop or isolated cranial nerve palsies

Diabetic Dyslipidemia: increased blood level of triglycerides & LDL & decreased levels of HDL

Increased Susceptibility to Infections: due to defective neutrophil functions & impaired cytokine production by macrophages

$\rightarrow$ susceptibility to skin infections, tuberculosis, pneumonia, pyelonephritis.