Pathology of Endocrine Organs
Part 1.

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Overview

1. Pathology of endocrine organs
   - Pituitary gland
   - Pineal gland
   - Thyroid gland (see next lecture!)
   - Parathyroid glands
   - Adrenal glands
   - Endocrine pancreas
   - Sex-cord stroma

2. General aspects of neuroendocrine tumors of non-endocrine organs (DNES)

3. Syndromes associated with endocrine tumors
Pathology of endocrine organs

Endocrinological classification (pathophysiology)

• Causes and consequences of decreased/no hormone function (=hypo...ism)
  • Underproduction
  • No effect
• Causes and consequences of increased hormone function (=hyper...ism)
  • Overproduction

Morphological classification (pathology)

• Congenital disorders
• Adaptive disorders
• Circulatory disorders
• Inflammatory disorders
• Neoplasia
Special issues in endocrine pathology

- **Congenital disorders=enzimopathies**
  - Inappropriate hormone production
  - No effective hormone function
  - No feedback

- Examples: dyshormonogenetic goiter, adrenogenital syndrome
Special issues in endocrine pathology

- **Adaptive disorders**
  - Primary hyperfunction = autonomous hormone production
  - Secondary hyperfunction = excessive release of regulating hormone/factor
    - Central
    - Ectopic (paraneoplasia)
  - Tertiary hyperfunction = secondary hyperfunction with an autonomous population

\begin{align*}
\text{Primary HF} & \quad \text{organ} \to \text{atrophy} \\
\text{Secondary HF} & \quad \text{organ} \to \text{hyperplasia}
\end{align*}
Special issues in endocrine pathology

• **Circulatory disorders**
  • Very rare = small organs with rich vascularisation
  • Ischemia can occur in the pituitary gland due to its limited space

• **Inflammations**
  • Almost always of autoimmune etiology
  • T-cell mediated (type IV) eg. diabetes mellitus type 1, autoimmune adrenalitis
  • Antibody mediated (type II) → acts as a regulating hormon eg. Graves disease
  • Infections affecting endocrine organs are very rare
Special issues in endocrine pathology

• **Neoplasias**
  
  *Origin*
  
  • Endocrine: thyroid follicles, adrenal cortex, sex-cord stroma
  • Neuroendocrine (tumors with neurosecretory features-see later): pituitary gland, thyroid C-cells, parathyroid glands, adrenal medulla, gastro-entero-pancreatic and other neuroendocrine cells of respiratory, urinary tract, skin etc. (GEP/DNES)

  *Dignity*
  
  • Classic cytomorphologic criteria of malignancy is NOT valid in endocrine organs!
  • Atypia, polymorphism, bizarre cells are more often found in hyperactivity than in malignancies!
  • *Exception:* *papillary thyroid carcinoma* → *diagnosis based on unique cytological features*
  • Criteria of endocrine malignancy in general: **local/vascular invasion and/or metastasis**
  • Neuroendocrine tumors are potentially malignant irrelevant to their microscopic morphology (see DNES tumor classification)
1. Adrenal cortical adenoma with bizarre cells
2. Hashimoto thyroiditis with Hürthle cells
3. Parathyroid adenoma with bizarre cells
4. Medullary thyroid carcinoma
Pituitary gland \((p1098)\)

- **Anatomy**
  - Anterior lobe (adenohypophysis)
  - Posterior lobe (neurohypophysis)

- **Note**: local mass effect may cause visual field abnormalities

- **Function:**
  - Anterior lobe
    - Somatotroph cells: GH
    - Lactotroph cells: prolactin
    - Corticotroph cells: ACTH
    - Thyrotroph cells: TSH
    - Gonadotroph cells: FSH, LH
  - Posterior lobe: ADH, oxytocin
Hyperpituitarism

• >99% adenomas
  • Microadenoma: <1 cm, macroadenoma: >1cm
  • Classification based on hormone secretion

  • Most common: prolactinoma  
    galactorrhea

  • Somatotroph adenoma  
    gigantism, acromegaly

  • Corticotroph adenoma  
    central Cushing syndrome

  • Other rare variants (gonadotroph, thyrotroph, nonfunctioning)
Morphology

Macro Adenoma

Micro
Normal: mixture of:
- acidophils (GH&PRL)
- basophils (ACTH, TSH, FSH&LH)
- Chromophobes

Adenomas: monotonous population
Hypopituitarism

• Physical damage
  • Mass lesion: adenoma
  • Trauma
  • Surgery, irradiation

• Vascular disorders
  • Pituitary apoplexy (rare cause of sudden death)
  • Sheehan syndrome (ischemic necrosis in pregnant women)

• Genetic defects
• Hypothalamic hormone deficiency (eg. suprasellar tumors)
• Infections (rare, granulomatous, eg. TB, sarcoidosis)

All kind of pituitary damage may result in empty sella syndrome
Posterior pituitary syndromes

• Hyperfunction
  • Syndrome of inappropriate ADH (SIADH)
  • Generally ectopic ADH secretion=paraneoplasia (small cell lung carcinoma)

• Hypofunction
  • Diabetes insipidus
  • Trauma, tumor etc.
Pineal gland

- Tumors
  - Pinealoma – deriving from pinealocytes, no special hormonal syndrome
  - Interestingly most of pineal gland tumors are of germ cell origin (eg. teratoma)
**Parathyroid glands** (p1126)

- **Anatomy**
  - 2 x paired organs
  - Rarely mediastinal location (intrathymic)
  - Histologically 3 different cell types (chief, water clear, oxyphil)

- **Function**
  - Parathormone release
  - Directly controlled by blood Ca 2+
  - Very short half life – Ca 2+ level is suitable to monitorize PTH release
Hyperparathyreoidism, hypercalcemia

• Primary (PHPT)
  • 90% adenoma, 9% hyperplasia (MEN), 1% carcinoma
  • Usually solitary lesion
  • Preoperative diagnosis: Radionuclide scan/FNAB
  • Surgery: intraoperative Ca 2+ test!

• Secondary
  • Cause: excessive Ca 2+ loss
  • Chronic renal failure
  • Hyperplastic change in all glands

• Malignancy associated hypercalcemia – PTH related protein (PTH-rP)
  • Common paraneoplasia with poor prognosis
  • Solid tumors: lung-head&neck squamous cell carcinoma, breast carcinoma, renal cell carcinoma
  • Hematologic malignancy: multiple myeloma
Morphology

- adenoma
- hyperplasia

normal parathyroid gland
Micro morphology

normal

adenoma
Consequences of hyperparathyreoidism

• Increased osteoclast activity
  • Skeletal lesions: osteitis fibrosa cystica, „brown tumor”

• Elevated Ca 2+ level
  • Repeating nephrolithiasis
  • Gastrointestinal malfunction (constipation)
  • CNS: depression
  • Neuromuscular: weakness
  • Cardial disorders: valvular calcification
Hypoparathyreoidism

- Generally iatrogenic (total thyreoidectomy)
- Autoimmune parathyreoiditis
- Genetic disorders
- Aplasia

- Consequences: decreased Ca 2+ level
  - Tetany, anxiety-depression, ocular and dental disorders, heart conduction abnormalities etc.
Adrenal glands (p1148)

• Anatomy
  • Paired organs
  • Rarely ectopic=eg. funicular
  • Different development (mesodermic&neuroectodermic)

• Function
  • Cortex: steroid hormones
    • Glucocorticoids
    • Mineralocorticoids
    • Sex steroids
  • Medulla: catecholamines
Adrenocortical hyperfunction

**Cushing syndrome = hypercortisolism**
- Central (=Cushing disease)
  - Pituitary corticotroph adenoma
  - Secondary hypercortisolism (ACTH↑, cortisol↑)
  - Diffuse adrenal hyperplasia
- Peripheral Cushing syndrome
  - Primary adrenal nodular hyperplasia or adenoma, rarely carcinoma
  - Primary hypercortisolism (ACTH↓, cortisol↑)
  - Adrenal cortex atrophy
- Ectopic Cushing syndrome
  - Paraneoplasia, eg. SCLC
  - Secondary hypercortisolism (ACTH ↑ ↑ ↑, cortisol↑)
  - Diffuse adrenal hyperplasia
- Exogenous Cushing syndrome
  - Glucocorticoid medication generally for immunosuppressive purpose

**Conn syndrome = hyperaldosteronism**
- primary adrenal adenoma
- rarely nodular hyperplasia
- Secondary hyperaldosteronism
  - Increased renin level: renal hypoperfusion, pregnancy
  - Renin producing tumors: very rare

**Hyperfunction of sex hormones**
- Malignant cortical neoplasia
- Adrenogenital syndrome
Adrenocortical hyperfunction - symptoms

Cushing syndrome = hypercortisolism

Conn syndrome = hyperaldosteronism
  - No external signs

Hyperfunction of sex hormones
  - Virilization, feminization

Cushing's Disease or Syndrome Symptoms

- Personality Changes
- Red Face
- Susceptibility to infection
  - Males: Gynecomastia
  - Females: Amenorrhea, Hirsutism
- Fat Deposition on Abdomen and Back of Neck ("Buffalo Hump")
- Osteoporosis (increased risk of fractures)
  - Fat Round "Moon" Face
  - CNS irritability
  - Fluid Retention (Edema)
  - Thin Extremities
  - GI Distress - T Acid
  - Purple Striae
  - Thin Skin
  - Bruises & Petechiae
Morphology of adrenal cortical lesions

- Adenoma
- Primary nodular
- Secondary diffuse
- Hyperplasia
Microscopic morphology

zona glomerulosa
zona fasciculata
zona reticularis

normal cortex
adenoma
Adrenocortical insufficiency

Primary

- Genetic abnormality
  - adrenogenital syndrome = 21 hydroxylase deficiency
  - mineralocorticoids ↓, glucocorticoids ↓, sex steroids ↑
  - ACTH ↑ ↑ ↑
  - Super-sized adrenals

- Congenital hypoplasia

- Acute hemorrhagic necrosis
  = Waterhouse-Friderichsen syndrome (meningococcus sepsis)

- Primary chronic adrenocortical insufficiency = Addison disease
  - ACTH ↑ and POMC ↑ (= hyperpigmentation)
    - Autoimmune adrenalitis
    - Infections (fungal, TB)
    - Metastatic cancer, lymphoma

Secondary

- ACTH deficiency
  - Hypopituitarism
  - Long term steroid administration = atrophy
    → Addison symptoms without hyperpigmentation
Adrenal medulla

• Pheochromocytoma
  • >90% hormonally active=secondary hypertension
  • >90% benign clinical course (no evident histological signs of malignancy)
  • Frequent germline genetic abnormalities: >10% (see later)
Morphology

Ganglion-like chief cells and sustentacular cells form „zellballen“
Embryonal type medullary tumors

- Neuroblastoma (see childhood tumors)

- Mature form: ganglioneurinoma – incidental, hormonally inactive tumor in adults
Hormonally inactive adrenal tumors

• Incidental cortical adenoma
  • Most frequent autopsy finding within the adrenals

• Metastatic malignancies
  • Lung-, kidney-, breast-, colorectal carcinoma, melanoma
Endocrine pancreas

• Anatomy
  • Islets of Langerhans are not visible macroscopically

• Function
  • β-cells: insulin production
  • α-cells: glucagon production
  • δ-cells: somatostatin
  • Other hormone products: pancreatic polypeptide, vasoactive intestinal polypeptide, gastrin
Hyperfunction of endocrine pancreas

- Always primary – generally hormonally active neuroendocrine tumors
  - Hyperinsulinism: insulinoma (generally benign), rarely islet hyperplasia (nesidioblastosis) → hypoglycemia
  - Glucagonoma → diabetes, characteristic skin lesion (necrolytic migratory erythema)
  - Gastrinoma → Zollinger-Ellison syndrome
  - VIPoma → WDHA syndrome (= watery diarrhea, hypokalemia, achlorhydria)

- General tumor features: see NET classification
Hypofunction of endocrine pancreas

• Diabetes mellitus (DM) is a group of metabolic disorders caused by hyperglycemia which is a result of defect in insulin secretion or insulin action or both
• Hyperglycemia is not a morphological disorder thus DM is a clinical diagnosis
• Classification of DM also based on clinical tests – morphology of endocrine pancreas is not examined routinely
• Pathology studies focus on the late morphological consequences of DM (generally faced them in the autopsy hall)
Classification of DM (p1132)

- Mixed insulin resistance and β-cell dysfunction: type 2 DM
- Inflammatory
  - Autoimmune T-cell mediated (hypersensitivity type IV): DM type 1
  - Infective: very rare (CMV)
- Exocrine pancreas defect (pancreatogenic DM)
  - Chronic pancreatitis
  - Total pancreatectomy
- Gestational DM
- Endocrinopathies (eg. Cushing syndrome)
- Drugs
- Genetic causes
Basic problems resulted from

1. **Glycation**
2. **PKC (protein kinase C) activation and**
3. **Intracellular hyperglycemia**

These problems result in → degeneration of:

1. Arterial intima (endothelial injury)
2. Arterioles
3. Basement membrane
4. Retina, lenses
5. Nerves

+ Increased risk of infections
Target organs affected by DM and its morphology (p1139-43)
Macrovascular Disease

- Accelerated atherosclerosis
  - DM is one (but not the only!) of the most important risk factors of atherosclerosis

- PAD: Peripheral Artery Disease
  - Commonly affect legs
Cardiac complications

• AMI – accelerates coronary sclerosis

• Valvular and mitral annulus calcification
„Diabetic foot”

• Gangrene and skin ulcers from
  • PAD
  • Microangiopathy
  • Neuropathy
  • Infections
Renal complication

- Micro- and macroangiopathy
- Glomerular damage
  - Nodular glomerulosclerosis = Kimmelstiel-Wilson disease
  - Diffuse mesangial sclerosis

- Pyelonephritis
  - Acute PN with necrotizing papillitis
  - Chronic PN

- End stage kidney
Kimmelstiel-Wilson disease  (see nephropathology lecture)
Eye disorders

• Diabetic retinopathy
  • Proliferative microangiopathy
  • Microhemorrhages
  • Fibrosis
• Cataract
• Glaucoma
### Infections in DM

**Rhinocerebral mucormycosis**

**TABLE 1. CLINICAL FEATURES, DIAGNOSIS, AND CAUSATIVE ORGANISMS OF SELECTED INFECTIONS IN PATIENTS WITH DIABETES.**

<table>
<thead>
<tr>
<th>Infection</th>
<th>Clinical Features</th>
<th>Diagnostic Procedure*</th>
<th>Organisms</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory tract</td>
<td>Cough, fever</td>
<td>Chest radiography</td>
<td>S. pneumoniae, S. aureus, H. influenzae, other gram-negative bacilli, atypical pathogens</td>
<td>Pneumococcal infection carries a higher risk of death in diabetic than in nondiabetic patients</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>Increased urinary frequency, dysuria, suprapubic pain</td>
<td>Urine culture</td>
<td>E. coli, Proteus species</td>
<td>Bacteriuria more common in diabetic than in nondiabetic women</td>
</tr>
<tr>
<td>Acute pyelonephritis</td>
<td>Fever, flank pain</td>
<td>Urine culture</td>
<td>E. coli, other gram-negative bacilli</td>
<td>Emphysematous infection should be considered.</td>
</tr>
<tr>
<td>Acute pyelonephritis</td>
<td>Fever, flank pain, poor response to antibiotics</td>
<td>Radiography or CT imaging</td>
<td>E. coli, other gram-negative bacilli</td>
<td>Emergency nephrectomy often recommended.</td>
</tr>
<tr>
<td>Perinphric abscess</td>
<td>Fever, flank pain, poor response to antibiotics</td>
<td>Ultrasonography or CT scanning</td>
<td>E. coli, other gram-negative bacilli</td>
<td>Surgical drainage usually required.</td>
</tr>
<tr>
<td>Fungal cystitis</td>
<td>Same as for acute bacterial cystitis</td>
<td>Urine culture</td>
<td>Candida species</td>
<td>Difficult to distinguish colonization from infection.</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>Local pain, redness, crepitus, bullous skin lesions</td>
<td>Radiography or CT imaging</td>
<td>Gram-negative bacilli, anaerobes (type I), or group A streptococcus (type II)</td>
<td>High mortality; emergency surgery required.</td>
</tr>
<tr>
<td>Necrotizing fasciitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive otitis externa</td>
<td>Ear pain, ototraheal, hearing loss, cellulitis</td>
<td>Clinical examination, magnetic resonance imaging</td>
<td>Pseudomonas aeruginosa</td>
<td>Prompt otoharyngologic consultation recommended.</td>
</tr>
<tr>
<td>Rhinocerebral mucormycosis</td>
<td>Facial or ocular pain, fever, lethargy, black nasal eschar</td>
<td>Clinical examination, magnetic resonance imaging, pathological findings</td>
<td>Mucor and rhizopus species</td>
<td>Strong association with ketoacidotic; emergency surgery required.</td>
</tr>
<tr>
<td>Abdomen</td>
<td>Fever, right upper quadrant abdominal pain, systemic toxicity</td>
<td>Radiography</td>
<td>Gram-negative bacilli, anaerobes</td>
<td>High mortality; gallstones in 50%; emergency cholecystectomy required.</td>
</tr>
</tbody>
</table>

*CT denotes computed tomography.
†Foot infections are described in detail in Table 3.

Sex cord stromal neoplasias *(p1050 and 992)*
Hyperfunction of sexual hormones: see adrenal cortical hyperfunction

- **Ovarian tumors**
  - Granulosa-Theca cell tumors
    - Hyperestrogenism may cause endometrial HP and carcinoma!
  - Fibroma/thecoma
    - Usually incidental, hormonally inactive
  - Sertoli-Leydig cell tumors
    - hyperandrogenism

- **Testicular tumors**
  - Leydig cell tumor
    - Precocity in childhood
  - Sertoli cell tumor
General aspects of neuroendocrine tumors of non-endocrine organs (DNES)

• Deriving from dispersed neuroendocrine cells of epithelial tissues (aka APUD cells)
• Diagnostic criterion: presence of at least 1 NE marker immunohistochemically

• Gastro-Entero-Pancreatic NeuroEndocrine Tumors (GEP-NET)
  • WHO classification of GEP-NET 2010
    • Neuroendocrine tumor, grade 1-3 (based on mitotic count/Ki67 index)
    • Neuroendocrine carcinoma grade 3 (based on morphology)

• Neuroendocrine tumors of the lung
  • WHO classification of lung tumors 2015
    • Typical/atypical carcinoid
    • Small cell lung carcinoma (SCLC)
    • Large cell neuroendocrine carcinoma

• Others
  • Urinary tract
  • Skin
  • Breast
Morphology of NE differentiation in tumors

NE differentiation present:
1. Insular structures common
2. Salt&pepper chromatin
3. Plasmocytoid appearance
4. Low mitotic count
5. No necrosis

Poorly differentiated neuroendocrine carcinoma (small cell type)
1. Hyperchromasia
2. Polymorphism
3. High mitotic count
4. Necrosis
Presence of neurosecretory granules

IHC (chromogranin A)

EM
Grading of GEP-NETs

• Grade 1: Ki 67:<2%, mitoses: <2/10 HPF

• Grade 2: Ki 67: 2-10%, mitoses 2-10/10 HPF

• Grade 3: Ki 67: >20%, mitoses >10/10 HPF
<table>
<thead>
<tr>
<th>Organ</th>
<th>Clinical behaviour: slow progression even in metastatic stage</th>
<th>Poorly differentiated Clinical behaviour: poor prognosis, rapid progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreas</td>
<td>NET grade 1,2&lt;br&gt;Insulinoma: practically benign</td>
<td>NEC grade 3: poor prognosis</td>
</tr>
<tr>
<td>Stomach, duodenum</td>
<td>NET grade 1,2&lt;br&gt;• MEN 1 &amp; atrophic gastritis associated: good prognosis&lt;br&gt;• Sporadic: worse prognosis</td>
<td></td>
</tr>
<tr>
<td>Small bowel</td>
<td>NET grade 1,2,3: high metastatic potential</td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>Rectum: grade 1,2: good prognosis</td>
<td>Proximal colon: NEC grade 3: poor prognosis</td>
</tr>
<tr>
<td>Appendix</td>
<td>NET grade 1: usually incidental finding in appendectomy: good prognosis</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>Typical/atypical carcinoid: indolent clinical course</td>
<td>NEC (small/large cell): poor prognosis&lt;br&gt;• Frequent paraneoplastic hormon secretion</td>
</tr>
<tr>
<td>Urinary tract</td>
<td></td>
<td>NEC: poor prognosis</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
<td>Merkel cell carcinoma: highly aggressive</td>
</tr>
<tr>
<td>Breast</td>
<td>Generally ER positive&lt;br&gt;Prognosis not differ from usual breast cancer</td>
<td></td>
</tr>
</tbody>
</table>
### Syndromes associated with endocrine tumors

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Mutated gene</th>
<th>Tumor types</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple endocrine neoplasia (MEN) type 1</td>
<td>MEN1</td>
<td>Parathyroid (PHPT) Pancreas Pituitary Gastric and duodenal gastrinomas (multiple)</td>
<td>Poor if NEC occur (mainly of pancreas)</td>
</tr>
<tr>
<td>MEN type 2</td>
<td>RET</td>
<td>2A: Parathyroid hyperplasia, phaeochromocytoma, medullary thyroid carcinoma</td>
<td>Good if preventive thyreoidectomy performed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Preventive thyroidectomy needed in childhood</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• Pheochromocytomas are usually benign</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>2B: plus neuromas and marfanoid habitus</td>
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<td></td>
<td></td>
<td>Familial medullary thyroid cancer</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• Only MTC occur</td>
<td></td>
</tr>
<tr>
<td>VHL</td>
<td>VHL</td>
<td>Phaeochromocytoma</td>
<td>Other cancer types (renal cell carcinoma)</td>
</tr>
<tr>
<td>Neurofibromatosis</td>
<td>NF1</td>
<td>Phaeochromocytoma</td>
<td></td>
</tr>
<tr>
<td>Familial paraganglioma (more types)</td>
<td>SDH (succinil dehydrogenase)</td>
<td>Phaeochromocytoma</td>
<td>Frequently malignant phaeochromocytoma</td>
</tr>
</tbody>
</table>
References

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• www.nejm.org/doi/full/10.1056/NEJM199912163412507
In memory of dr. Illyés György (Gyuri)
1955-2017