ENDOCRINOLOGICAL PARANEOPLASTIC SYNDROME

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Content:

- Definition
- General features
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- Cushing's syndrome
- Tumour induced hypoglycemia
- Investigations

Definition

Disorders that accompany benign or malignant tumor
but are not directly related to mass effects or invasion

General features

- Excess hormone production from an **atypical tissue source**
- Documentation of tumor hormone production based on **immunostaining, mRNA production, or hormone secretion in vitro**
- **Hormone gradient** across the tumor vascular supply
- Resolution or **decline of hormone levels** after reduction of tumor mass.

TABLE 98-1 Paraneoplastic Syndromes Caused by Ectopic Hormone Production

PARANEOPLASTIC SYNDROME	ECTOPIC HORMONE	TYPICAL TUMOR TYPES[a]
Common		
Hypercalcemia of malignancy	Parathyroid hormone–related protein (PTHrP)	Squamous cell (head and neck, lung, skin), breast, genitourinary, gastrointestinal; osteolytic metastases
	1,25-Dihydroxyvitamin D	Lymphomas
	Parathyroid hormone (PTH) (rare)	Lung, ovary
	Prostaglandin E_2 (PGE_2) (rare)	Renal, lung
Syndrome of inappropriate antidiuretic hormone secretion (SIADH)	Vasopressin	Lung (squamous, small cell), gastrointestinal, genitourinary, breast, ovary
Cushing's syndrome	Adrenocorticotropic hormone (ACTH)	Lung (small cell, bronchial carcinoid, adenocarcinoma, squamous), thymus, pancreatic islet, medullary thyroid carcinoma, pheochromocytoma
	Corticotropin-releasing hormone (CRH) (rare)	Pancreatic islet, carcinoid, lung, prostate
	Ectopic expression of gastric inhibitory peptide (GIP), luteinizing hormone (LH)/human chorionic gonadotropin (hCG), other G protein–coupled receptors (rare)	Macronodular adrenal hyperplasia
Less Common		
Non–islet cell hypoglycemia	Insulin-like growth factor type II (IGF-II)	Mesenchymal tumors, sarcomas, adrenal, hepatic, gastrointestinal, kidney, prostate
	Insulin (rare)	Cervix (small-cell carcinoma)
Male feminization	hCG[b]	Testis (embryonal, seminomas), germinomas, choriocarcinoma, lung, hepatic, pancreatic islet
Diarrhea or intestinal hypermotility	Calcitonin[c]	Lung, colon, breast, medullary thyroid carcinoma
	Vasoactive intestinal peptide (VIP)	Pancreas, pheochromocytoma, esophagus
Rare		
Oncogenic osteomalacia	Fibroblast growth factor 23 (FGF23) or phosphatonin	Hemangiopericytomas, osteoblastomas, fibromas, sarcomas, giant cell tumors, prostate, lung
Acromegaly	Growth hormone–releasing hormone (GHRH)	Pancreatic islet, bronchial, and other carcinoids
	Growth hormone (GH)	Lung, pancreatic islet
Hyperthyroidism	Thyroid-stimulating hormone (TSH)	Hydatidiform mole, embryonal tumors, struma ovarii
Hypertension	Renin	Juxtaglomerular tumors, kidney, lung, pancreas, ovary
Consumptive hypothyroidism	Type 3 deiodinase	Hepatic and other hemangiomas
Cancer immunotherapy associated autoimmune diseases	Autoimmune hormone deficiencies Thyroiditis, Graves' disease	Cancers treated with immunotherapy, particularly anti–CTLA-4, PD-1, PD-L1

Humoral hypercalcemia of malignancy:

- Common in cancers of the lung, head and neck, skin, esophagus, breast, and genitourinary tract and in multiple myeloma and lymphomas
- **Causes**: * Overproduction of PTHrP

  * Excess production of 1,25-dihydroxyvitamin D.
- PTHrP is structurally related to PTH and binds to the PTH receptor,
- Lymphomas can produce an enzyme that converts 25-hydroxyvitamin D to active 1,25-dihydroxyvitamin D.

Symptoms

- Usually asymptomatic
- If symptomatic

  Fatigue, mental status changes, polyuria, dehydration, or symptoms of nephrolithiasis
- **ECG changes:**

  ShortST segments and QT intervals, as well as bundle branch blocks and bradyarrhythmias.

HHM	Hyperparathyroidism
• Known malignancy • Recent onset of hypercalcemia • Very high serum calcium levels	
Metabolic alkalosis	Hyperchloremic acidosis
• PTHrP elevated • PTH suppressed	• PTH elevated

Treatment

- **Saline rehydration** (typically 200–500 mL/h) to dilute serum calcium promotes calciuresis
- Forced diuresis with **furosemide** (20–80 mg IV in escalating doses)
- **Bisphosphonates** such as zoledronate (4–8 mg IV), pamidronate (60–90 mg IV), and etidro-nate (7.5 mg/kg per day orally [PO] for 3–7 consecutive days) can reduce serum calcium
- **Other drugs** include: Denosumab, Cinacalcet
- **Glucocorticoid treatment:** Lymphomas, multiple myeloma, or leukemias
- **Dialysis**- severe hypercalcemia when saline hydration and bisphosphonate treatments are not possible or are too slow in onset.

TUMOR-ASSOCIATED SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE

- **Cause:** Ectopic vasopressin production
- **Tumours with neuroendocrine features:** SCLC and carcinoids
- Other forms of lung cancer and with CNS lesions, head and neck cancer, and genitourinary, gastrointestinal, and ovarian cancers
- Other causes of hyponatremia should be excluded
- Hyponatremia and reduced serum osmolality with inappropriately normal or increased urine osmolality.

Symptoms:

- Mostly asymptomatic
- If symptomatic weakness, lethargy, nausea, confusion, depressed mental status, and seizures may be present.

Treatment

- Should be corrected **gradually**
- **Rapid correction** can cause brain dehydration and **central pontine myelinolysis.**
- **Fluid restriction** to less than urine output plus insensible losses.
- **V2-receptor antagonists**, tolvaptan (15 mg PO daily) or conivaptan (20–120 mg PO bid or 10–40 mg IV) - **euvolemic hyponatremia**
- **Severe hyponatremia** (Na <115 meq/L) or mental status changes- **hypertonic (3%) or normal saline infusion with furosemide** to enhance free water clearance
- **Demeclocycline** (150–300 mg orally 3–4 times daily) can be used to inhibit vasopressin action on the renal distal tubule

CUSHING'S SYNDROME

- Common in neuroendocrine tumors.
- SCLC is the most common cause of ectopic ACTH
- Others include bronchial and thymic carcinoids, islet cell tumors, other carcinoids, and pheochromocytomas.
- **Cause**: Increased expression of the proopiomelanocortin (POMC) gene, which encodes ACTH, MSH, other peptides

Symptoms

- Less marked weight gain and fat redistribution.
- Fluid retention, hypertension, hypokalemia, metabolic alkalosis, glucose intolerance and steroid psychosis
- Increased pigmentation due to high ACTH
- Skin fragility and easy bruising
- Severe hypokalemia

Cushing's disease	Ectopic ACTH
• Weight gain	• Weight gain may be absent
• Hypertension-50%	• Hypertension- 75%
• Hypokalemia absent	• Hypokalemia present
• High dose dexamethasone suppression test: suppressed	• High dose dexamethasone suppression test: not suppressed

Treatment

- Treatment of the underlying malignancy may reduce ACTH levels but is rarely sufficient to reduce cortisol levels to normal.
- Drugs include ketoconazole, metyrapone, mitotane, etomidate
- Glucocorticoid replacement should be provided to prevent adrenal insufficiency

TUMOR-INDUCED HYPOGLYCEMIA

- **Cause:** Excessive amounts of insulin-like growth factor type II (IGF-II)
- Mesenchymal tumors, hemangiopericytomas, hepatocellular tumors, adrenal carcinomas

Diagnosis

- Low serum glucose, suppressed insulin levels with symptoms of hypoglycemia.
- Serum IGF-II levels may not be increased but an elevated IGF-II/IGF-I ratio greater than 10:1 is suggestive.

Treatment:

- Frequent meals and IV glucose, are necessary to prevent hypoglycemia.
- **DRUGS**: Glucagon, recombinant GH, and glucocorticoids.

HUMAN CHORIONIC GONADOTROPIN

- Testicular embryonal tumors, germ cell tumors, extragonadal germinomas, lung cancer, hepatoma, and pancreatic islet tumors.
- **Men**- Precocious puberty in boys or gynecomastia
- **Women**- asymptomatic

ONCOGENIC OSTEOMALACIA

- **CAUSE:** Excessive production of fibroblast growth factor 23 (FGF23)
- FGF23 inhibits the renal conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D
- Reduced serum phosphorus and renal phosphate wasting, leading to muscle weakness, bone pain, and osteomalacia.
- **Treatment:** Removal of the tumor and supplementation with phosphate and vitamin D.
- Burosumab: monoclonal antibody against FGF23

Investigations:

- Computed tomography (CT)
- Magnetic resonance imaging (MRI)
- Positron emission tomography (PET)
- Octreotide scintigraphy

Treatment of the underlying tumor is the mainstay of all paraneoplastic endocrine syndromes.

Depending on the hormone produced, specific therapies can be used to ameliorate symptoms but rarely influence overall survival or cancer progression.

THANK YOU