Paraneoplastic Syndromes

Resource: 1. ***Harrison's Principles of Internal Medicine****, Vol.1, 18th ed.; "Paraneoplastic syndromes," pg. 827-838; Longo, Fauci, Kasper, Hauser, Jameson, Localzo et all.; Mc Graw Hill, 2012. 2.* ***Davidson's Principles & Practice of Medicine****, 22nd ed., "Oncology," pg. 259-283.; Compiled by Andrei Cociug, © 2020.*

Definition	In addition to local tissue invasion and metastasis, neoplasms can produce a variety of products that can stimulate hormonal, haematological, dermatologic and neurologic responses. **Paraneoplastic syndrome** = "disorders that accompany benign or malignant Tu. but are not directly related to mass effect or invasion." The most common are as such: A. Endocrine paraneoplastic sy.: B. Haematological C. Neurological D. Neuromusculoskeletal E. Cutaneous

A) Endocrine Paraneoplastic Syndromes: Aetiology

Paraneoplastic syndrome	Ectopic hormone	Tumour types
Common		
Hypercalcemia of malignancy (HM)	PTH-related protein (PTHrP)	SCC (H&N; Lung; Skin), Breast, GU & GI CA.
	1,25 dihydroxyvitamin D	Lymphomas
SIADH (Syndrome of inappropriate ADH secretion)	Vasopressin (ADH)	Lung CA (SCC; Small Cell), GI, GU & Ovarian CA.
Cushing syndrome (10-20% of cases of Cushing syndrome cases are due to ectopic ACTH production.)	ACTH	Lung CA (**Small Cell** [50% of cases]; Bronchial carcinoid; Adenocarcinoma; SCC), **Thymus** [15%], Pancreatic islet, Medullary thyroid CA.
	CRH & other hormones are rare.	

Less Common paraneoplastic syndromes incl.:

- Tumour-induced hypoglycaemia (caused by ectopic secretion of IGF or Insulin)
- Male feminisation (hCG-secreting Tu.)
- Diarrhoea or interstitial hypermotility (Calcitotin- & VIP-secreting Tu.)

Rare paraneoplastic syndromes incl.:

- Oncogenic osteomalacia (FGF23-secreting Tu.), aka Tumour-induced osteomalacia (marked softening of the bones.) Usually caused by mesenchymal tumours.
    - Characterised by markedly ↓ serum [PO_4^{3-}], muscle weakness, and bone pain.
    - Serum [Ca^{2+}] and PTH levels are normal, whilst 1,25 dihyrdroxyvitamin D is low.
    - Resection of the tumour reverses the disorder.
- Acromegaly (GNRH- or GH-secreting Tu.)
- Hyperthyroidism (TSH-secreting Tu.)
- Hypertension (Renin-secreting Tu.)

*Legend: CA = Cancers; Tu. = Tumour; H&N = Head and Neck; GU = Genitourinary; GI = Gastrointestinal; FGF23 = Fibroblast-growth factor 23.

A) Endocrine Paraneoplastic Syndromes: Dx. & Treatment		
Paraneoplastic syndrome	**Dx.**	**Tx.**
Hypercalcemia of malignancy (HM)	• Usually incidental (no clinical features beforehand) • When serum [Ca^{2+}] is > 3.5 mmol/L, Pz. may experience fatigue, mental status changes, dehydration, symptoms of nephrolithiasis. • Pz. present w. ↓ serum PTH level, hypophosphatemia, • ↑ serum 1,25 dihydroxyvitamin D or PTHrP	• Diet restrictions • Oral PO_4^{3-} and saline rehydration (to dilute the Ca^{2+} and replenish the phosphate) • ± Forced diuresis w. furosemide • Bisphosphonates (Zoledronate, 4-8 mg IV) • Dialysis should be considered in severe hypercalcaemia.
SIADH (Syndrome of inappropriate ADH secretion)	• Usually incidental (Pz. are asymptomatic, though their serum [Na^+] is ↓). • Symptoms may incl. weakness, lethargy, nausea, confusion, depressed mental status and seizures. • To confirm Dx. Exclude other causes of hyponatremia (renal, adrenal or thyroid insufficiency, physiologic compensatory mechanisms, etc.) ADH measurement is not usually necessary.	• Correct hyponatremia gradually (fluid restriction to less than urine output) unless mental status is altered or there is risk of seizures (which may req. infusion w. hypertonic solution – i.e. 3% saline). • Beware of the possible complication – central pontine myelinolysis – that occur w. rapid correction of [Na^+]
Cushing syndrome	• Pz. w. Cushing's due to ectopic ACTH production exhibit less marked symptoms (weight gain, centripetal fat redistribution, etc.) • A few distinct features incl.: marked fluid retention and hypertension, hypokalaemia & hypernatremia (due to the stimulation of aldosterone receptors,) metabolic alkalosis, glc. intolerance and occasionally psychosis (. • ↑ serum [ACTH] leads to ↑skin pigmentation. • ↑ urine [cortisol], ↑plasma [ACTH] irresponsive to glucocorticoid suppression are diagnostic.	• Pz. w. ectopic ACTH syndrome may experience depression or personality changes, they may have metabolic derangements (incl. DM), etc. • Poor wound healing and predisposition to infection can complicate causal surgical Tx. • Infections caused by opportunistic agents (e.g. Pneumocystis and mycoses are often the cause of death.) • Tx. should, like in every other cases, focus on the underlying malignancy. • Attempt to reduce [cortisol] w. ketoconazole, metyrapone and mitotane (dose tampered to maintain low cortisol prod.)

B) Haematologic Paraneoplastic Syndromes: Aetiology

NOTE: The elevation of granulocyte, platelet, and eosinophil counts in most Pz. w. myeloproliferative disorders is caused by the proliferation of the myeloid elements due to the underlying disease rather than a paraneoplastic syndrome.

Paraneoplastic syndrome	Ectopic hormone	Tumour types
Erythrocytosis	Erythropoietin (EPO)	Renal cancers (incidence: 3%), HCC (incidence: 10%), **Cerebellar haemangioma** (incidence: **15%**)
Granulocytosis (30% of Pz. w. solid Tu.)	Granulocyte Colony Stimulating factor (G-CSF) & IL-6	**Lung (incidence: 40%)**, GU, GI, Ovarian, Hodgkin's disease
Thrombocytosis (35% of Pz. w. thrombocytosis have cancer)	IL-6 ? Thrombopoietin (TPO)	**Lung (incidence: 40%)**, GI, Ovarian, Breast CA, Lymphoma
Eosinophilia (1% of Pz. w. cancer)	IL-5	Lung CA**, Lymphoma (incidence: 10%)**, Leukaemia
Thrombophlebitis (DVT and PE are the most common thrombotic cond. in Pz. w. cancer. 15% of Pz. w. thrombophlebitis have cancer)	Procoagulants and cytokines released from tumour cells or assoc. inflammatory cells.	Lung, GU, GI, Ovarian, Prostate, Breast CA, Lymphoma

B) Haematologic Paraneoplastic Syndromes: Dx. & Treatment

Paraneoplastic syndrome	Dx.	Tx.
Erythrocytosis	• ↑ HCT (>52% ♂ and > 48% in ♀) which can be detected on routine CBC. In most cases this is asymptomatic	• Cancer therapy • Phlebotomy may control any symptoms rel. to ↑ HCT
Granulocytosis	• Granulocyte count >8000 cells/mcL detected on routine CBC. Most Pz. are asymptomatic.	• Cancer therapy
Thrombocytosis	• Platelet count >400 000/mcL	• Cancer therapy
Eosinophilia	• Eosinophil count >5000 cells/mcL • Pz. may present w. shortness of breath (in the context of eosinophilic lung infiltrates.)	• Cancer therapy • Symptoms may be relieved by inhaled glucocorticoids.
Thrombophlebitis	• **Migratory or recurrent thrombophlebitis** may be the initial manifestation of cancer. The coexistence of peripheral venous thrombosis w. visceral carcinoma is called **Trousseau's syndrome**. • Dx. by DDimers, U/S & Venography ± CXR, ECG, CTA or V/Q scan.	• IV UFH or LMWH for > 5 days • Concomitant administration of warfarin (aim for INR 2 to 3.) for 3 months • Consider the placement of an inferior vena cava (Greenfield) filter in case anticoagulation Tx. Is CI • Breast CA Pz. req. prophylaxis Tx.

*Legend: mcL = microlitre;

C) Neurologic Paraneoplastic Syndromes: Aetiology

NOTE: PND (Paraneoplastic Neurologic Disorders) are cancer-related syndromes that can affect any part of the NS
In 60% of cases, the neurologic symptoms precede the cancer diagnosis.
PNDs affect about 2-3% of Pz. w. neuroblastoma or SCLC, and **30-50% of Pz. w. thymoma** or sclerotic myeloma.

Classic syndrome: Cancer-associated	**Non-classic syndrome:** May occur in the absence of cancer
• Encephalomyelitis (PEM) • Limbic encephalitis • Cerebellar degeneration (PCD) • Opsoclonus-Myoclonus • Gastrointestinal paresis • Lambert-Eaton myasthenic syndrome • Cancer-assoc. retinopathy	• Brainstem encephalitis • Stiff-person syndrome • Necrotising myelopathy • Motor neuron disease • Guilliam-Barre syndrome • Polymyositis • Subacute and chronic mixed sensory-motor neuropathy

Pathogenesis:

- Most PNDs are mediated by immune responses triggered by neuronal proteins (onconeuronal antigens) expressed by tumours.
- In PNDs of the CNS, many antibody-assoc. immune resp. have been identified. These Atbs. react w. the patient's Tu. and their detection in serum or CSF usually predicts the presence of cancer.
    - Disorders assoc. w. immune resp. against intracellular antigens are, unlike disorders assoc. w. immune resp. against surface antigens, less responsive to immunotherapy.

Cancer	Antibody	Associated PND
SCLC	**Against intracellular antigens**:	
	• Anti-Hu • Anti-CV	**Encephalomyelitis** • Inflammatory process w. multifocal involvement of the NS, incl. brain, brainstem, cerebellum and spinal cord.
	• Anti-Ri	**Cerebellar degeneration** • Usually preceded by dizziness, blurry or double vison, nausea and vomiting. • A few days-weeks later, Pz. Develop dysarthria, gait and limb ataxia, and variable dysphagia.
	• Anti-amphiphysin	**Stiff-person syndrome, Encephalomyelitis** • (see above)
	Against surface antigens	
	• Anti-AChR (neuronal)	**Autonomic neuropathy**
	• Anti-VGCC	**Cerebellar degeneration** • (see above)
	• Anti-AMPA R. • Anti-GABA R.	**Limbic encephalitis** • Inflammation of the temporal lobe(s) characterized by confusion, depression, agitation, anxiety, severe short-term memory deficits and seizures.

Cancer	Antibody	Associated PND
Thymoma	**Against intracellular antigens**:	
	• Anti-CV	**Encephalomyelitis** • See above
	Against surface antigens	
	• Anti-AChR (muscle)	**Myasthenia gravis**
	• Anti-VGKC	**Neuromyotonia**
	• Anti-AMPA R.	**Limbic encephalitis**

Dx.

- Three key concepts are imp. for the Dx. and management of PND
    1. Symptoms typically appear before the presence of a tumour is known
    2. The neurologic syndrome usually develops rapidly, producing severe deficits in a short time
    3. There is evidence that prompt tumour control improves the neurologic outcome
- Dx. is based on clinical, radiologic (esp. MRI), electrophysiologic and CSF findings (esp. pleocytosis.)
- Identify the antibodies responsible for the condition in blood or CSF
- Demonstrate the cancer

Tx.

- Involves infusion w. IVIg & Tu. Removal.

D) Cutaneous Manifestations of Cancer

Many cancers present w. skin manifestations that are not due to metastases

Sign/Symptom	Cancer
• Pruritus (= itch) ○ Symptomatic relief w. antihistamines and menthol-containing preparations.	• Polycythaemia Vera, Lymphoma, Leukaemia and CNS tumours
• Acanthosis nigricans ○ Formation of dark, velvety discolorations in body folds and creases (armpits, groin and neck.)	• May precede cancer by many years and is particularly assoc. w. gastric cancer.

• Vitiligo
  ○ Focal hypopigmentation
  ○ It's indicated to protect the depigmented patches from sun exposure.
  ○ Narrowband UVB is the most effective re-pigmentary treatment
	• May be assoc. w. malignant melanoma, and is possib. due to an immune resp. to melanocytes.

• Pemphigus ○ Blistering disorder	• Lymphoma, Kaposi's sarcoma, and Thymic tumours
• Dermatitis herpetiformis ○ Autoimmune blistering disorder that is strongly assoc. w. gluten intolerance.	• May precede GI tumours (e.g. lymphoma, MALToma)