Paraneoplastic syndromes

- what are paraneoplastic syndromes?
  Paraneoplastic syndromes are different types of diseases that are associated with the presence of a tumor but that manifest in regions that are unrelated to the anatomical distribution of the tumor or its metastasis.
  They are present in up to 40% of cancer (mainly lung, GI, skin and blood cancers) patients and can develop at any stage of the neoplastic growth: preceding neoplasia diagnosis, corresponding to cell dissemination or tumor relapsing, or it can worsen the course of the disease itself.
- what are the main mechanisms of paraneoplastic syndrome?
  1. **excessive or ectopic production** of hormones, or other physiologically active compounds.
  2. **deficiency** of normal factors such as calcium or glucose
  3. **host** response to the tumor (main way in which neurological paraneoplastic syndrome presents)
- how are paraneoplastic syndromes classified?
  Paraneoplastic Syndromes can be roughly divided into two types:
  - **Simple paraneoplastic syndromes:** named after the particullar type of tissue where these diseases are present (neurologic, endocrine-metabolic, rheumatic, osteoarticular, dermatological, hematological, vascular and nephrological diseases).
  - **Complex paraneoplastic syndromes**: cachexia, anorexia, fever.
- A very general classification of the more frequent paraneoplastic syndromes depending on the type of the tissues is:
  - endocrine-metabolic: the most frequent (40%).
  - rheumatic-osteoarticular in more than 15% of patients.
  - dermatological in more than 15% of patients.
  - hematological-vascular in more than 15% of patients.
  - neurological disorders in more than 10% of patients.
  - nephrological only 5% of patients.
- describe endocrine paraneoplastic syndrome
  By definition, the responsible cancers are **not** of endocrine origin (≠ adenomas). So there's ectopic hormone production. Symptoms therefore might be similar or the same as endocrine diseases but the cause is different. The tumors that cause endocrine Pn. S. have a malignant phenotype.
  - The most common presentation is the Paraneoplastic Cushing syndrome
    - approximately 50% of the affected individuals have **small cell lung carcinoma**

        - excessive production of ACTH (by pituitary) and its precursor **pro-opiomelanocortin (POMC)**
            - in normal Cushing there is not an elevation in POMC.
            - POMC is associated with lipolysis in cachexia and leptin stimulates its production.
        - signs and symptoms are different too, due to rapid onset
            - there is no obesity or moon face, but rather **weight loss.**
            - high BP
            - Hypokalemia → muscle cramping and weakness
    - Paraneoplastic Hypercalcemia
      Hypercalcemia is probably the most common type of paraneoplastic syndrome, in fact, **symptomatic hypercalcemia is more often related to cancer than to hyperparathyroidism.**
      Associated cancers: T-cell lymphoma, multiple myeloma, squamous cell carcinoma of the lung
      Due to a production of IL-1 TGF-α, TNF-α and **Parathyroid-hormone related protein (PTHRP)** that acts like PTH (induces bone reabsorption and decreases renal calcium excretion) symptoms include confusion, lethargy, nausea, coma.
      osteolysis can also be induced by cancer, whether primary in the bone as in **multiple myeloma, or metastatic to bone.**
    - Paraneoplastic (SIADH)
      remember: vasopressin = ADH
      Major forms of underlying cancer: **small cell lung cancer, intracranial neoplasms.**
      Inappropriate release of ADH (even with euvolemia). SIADH is characterized by **absence of edema and hypervolemia**.
      As a result, there's
        - dilutional Hyponatremia ([Na+] < 135 mEq/L)
        - hypo-osmolarity in plasma *(less than 270 mOsm/L)*
        - urine hyperosmolarity.
        - other **clinical features** depending on the degree of hyponatremia and to its time and rate of onset include: **anorexia, nausea, vomiting, confusion, and seizures**.
    - Paraneoplastic Hypocalcemia
      related to **lung and breast carcinoma**
      Secretion of **calcitonin** inhibits reabsorption and increases the renal excretion of calcium
      Often asymptomatic. Sometimes tetany, fasciculation, *and* hyperreflexia.
    - Paraneoplastic Hypoglycemia
      20% in gastrointestinal tumors, 45% in mesenchymal tumors
      Production of **big IGF-II** that stimulates the entry of glucose into tumor cells by inhibiting hepatic glucose uptake.

    - Paraneoplastic acromegaly (very rare)
      due to the presence of **neuroendocrine tumors in the pancreas** (islet cells and others) or **bronchial carcinoids**.
      They secrete **GH Releasing Hormone** which increases the GH's production and secretion from the anterior pituitary lobe.
- what is the diagnostic criteria for endocrine-metabolic paraneoplastic syndrome?
    - To recognize an endocrine syndrome associated with a non-endocrine tumor
    - High blood/urinary levels of the hormone
    - Low blood levels of the hormone after tumor surgery
    - Absence of disease in the endocrine-related organ
    - Remission/recurrence of the syndrome with tumor treatment/ recurrence
    - Hormone gradient between tumor and peripheral vein: establishing a relationship (ratio) between tumor size/malignancy and hormone levels in the blood
    - Extraction of the hormone from neoplastic tissue
    - Determination of hormonal activity with biological, RIA (radio immuno assay), immunological tests (check the hormones are biologically active)
    - Biochemical characterization of peptides produced by the tumor (check if it's making precursor hormones)
    - In vitro demonstration of hormonal production by cancer
    - Identification of hormonal mRNA in the tissue or cell culture
- describe hematological paraneoplastic syndrome
  Hematological paraneoplastic syndromes commonly present with **anemias**, generally normocytic, normochromic with normal or slightly decreased iron and ferritin. And **coagulopathies.**
  There's different types
    - Coagulopathies:
      tumors activate clotting. Usually closer to the tumor site.
        - **disseminated intravascular coagulation (DIC):** cancer cells can release procoagulant substances or trigger the release of tissue factor, initiating a widespread activation of the blood clotting cascade throughout the body. This can complicate metastatic tumor course and is often present in **leukemias**and **prostate cancer**
        - **Trousseau's Syndrome** (thromboembolism) excessive mucins causing activation of ****serine proteases that activate factor X and trigger the coagulation pathway. Common in **pancreatic and lung cancer**
        - nonbacterial **thrombotic endocarditis** caused by hypercoagulability. Common in cancers where there's an

increased secretion of mucus that induces a thrombus and occludes the vessels: **lung adenocarcinoma, colon cancer and ovarian cancer.** If vessels in the brain are occluded there's **encephalopathy** and acute **neurological deficits**

- autoimmune hemolytic anemia
  Hemolytic anemia can be mediated by two types of antibodies:
  - "warm"antibodies(**IgG**),especially in the **B-cell lymphomas and leukemias:**
    - hemolysis is **extravascular** in the spleen by phagocytosis
  - "cold" antibodies (**IgM**),
    - **intravascular** hemolysis, in which antibodies attack red blood cells at low temperature.
- Signs and symptoms are related to small vessels' occlusion: acrocyanosis of hands, feet, or face (ears, nose).
- erythrocytosis
  Sometimes some tumors cause erythocytosis due to the **ectopic synthesis of hematopoietic growth factors and erythropoietin.**
  Secondary erythrocytosis is related to:
  - cerebellar hemangioblastoma (20%)
  - renal adenoma and renal cyst (15%),
  - hepatocellular carcinoma (15%).
- leukemoid reaction
  there's excessive production of leukocytes induced by the **overproduction of**
  - granulocyte colony stimulating factor (**G-CSF)**
  - macrophage colony stimulating factor (**GM-CSF**)
  - **IL-3** and other interleukeins

- describe paraneoplastic syndrome of the kidney
  They are considered as autoimmune damage.
  They can be present in patients with **colon cancer, ovarian cancer, and lymphomas** due to circulating immune complexes.
  - **Paraneoplastic membrano-proliferative glomerulonephritis**
  - **Primary IgA nephropathy** (deposition of the IgA antibody in the glomerulus)
  - Focal glomerulosclerosis
  - **Nephrotic syndrome due to glomerulopathy** mimicking membrano-proliferative glomerulonephritis
- describe paraneoplastic neurological syndrome
  These are the main ones associated with the host immune response.
  Mostly related to small cell lung cancer
  - **Lambert-Eaton myasthenic syndrome** (main)
    - 70% associated with small cell lung cancer
    - it's an autoimmune calcium-channelopathy affecting *P*-type Ca++ *channel,* a type of **voltage-gated Ca++ *channel*:** anti-P/

Q antibodies→less Ca++ entry at nerve ending → less ACh release at the neuromuscular junction leading to
        - weakness of **proximal limbs** and occasionally in the muscles head and neck (**bulbar muscles**)
    - similar to **myasthenia gravis** (absence of the ACh receptors). The main difference is that in case of **repeated stimulation** of the muscles the strength of the **contraction increases** each time while this does not occur in case of myasthenia.
  - **Paraneoplastic encephalopathy**
    - small cell lung cancer, breast cancer
    - progressive **dementia**, mood swings, seizures, occasional focal sensory-motor impairment
    - **Anti-Neuronal Nuclear Autoantibodies (ANNA-1 and ANNA-2)** detected in the blood of some patients and react with a group of proteins that are located in the neuron nucleus.
  - **Paraneoplastic neuropathies**
    - small cell lung cancer
    - Including **Peripheral neuropathy** which is the more frequent long-distance effect produced by cancer on the peripheral nervous system
    - painful peripheral neuropathies, with sensory loss, proprioception loss and loss of vibratory sensation
    - variable degeneration of brainstem and cerebellum
    - Anxiety and depression, amnesia, dizziness, confusion, hallucination and behavioral abnormalities.
    - In some patients, ANNA-1 antibodies are detected
  - **Paraneoplastic cerebellar syndrome**
    - small cell lung cancer, ovarian cancer, breast cancer, Hodgkin's lymphona.
    - **severe ataxia** symmetric in the beginning and they become asymmetric.
    - Antibodies involved: Purkinje cell cytoplasmic antibody type 1 (anti-Yo or PCA1), Type 1 antineuronal nuclear antibody (anti-Hu or ANNA 1).
      - Basically, it is an immune response predominantly **against the Purkinje cells** of the cerebellum.
    - These syndromes usually do not respond to the treatment (including immunotherapies) because of an early T-cell-mediated destruction of the Purkinje cells occurs.
- describe paraneoplastic skin syndrome
  There are pigmented skin lesions or keratosis associated to cancer:
  1. **Acanthosis nigricans** (gastric cancer): thickened, hyperpigmented skin with a velvet-like texture in skin folds
  2. **Generalized melanosis** (lymphomas, melanoma, hepatocellular

carcinoma),
3. **Bowen's disease** (lung cancers, gastric cancers): in situ carcinoma that appears as a dark red eczematous plaque
4. **Sudden appearance of multiple seborrheic keratosis** (Leser-Trèlat sign) (lymphoma, GI cancers and melanoma)
5. **Sweet syndrome (acute febrile neutrophilic dermatosis)** fever, neutrophilia, erythematous nodules or plaques on the face and upper limbs.
6. **Palmar hyperkeratosis** (non Hodgkin lymphoma)
7. **Ichthyosis**: hyperkeratosis “fish-like skin” (Hodgkin lymphoma)