PARANEOPLASITC SYNDROMES

An Approach to Diagnosis and Treatment

ESO Course

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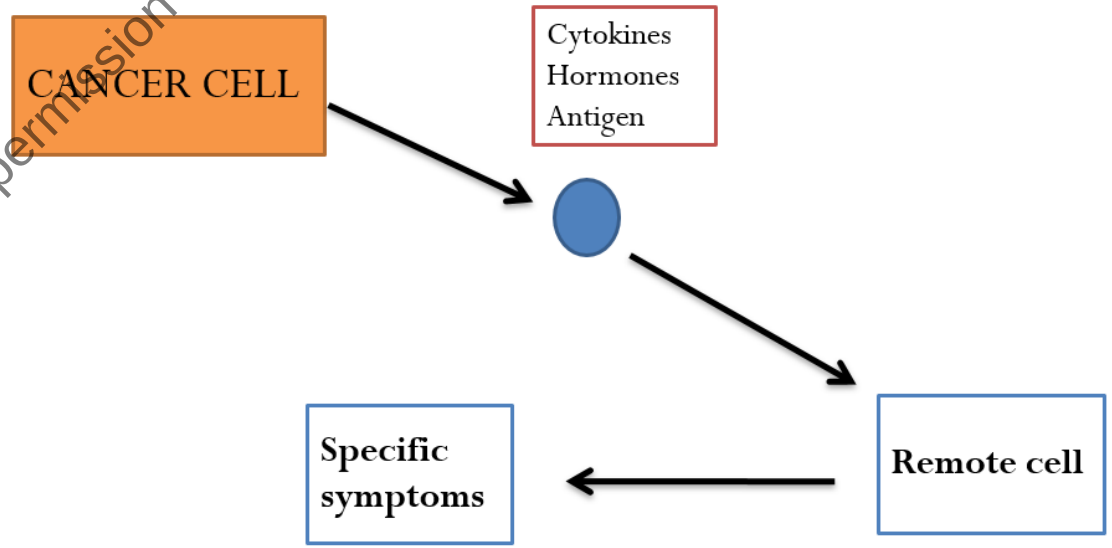
The content of the lecture

- The aim of present presentation is to:
  - Describe the definition of PNS
  - Describe the epidemiology and etiologies of PNS,
  - Cover the general principals of evaluation and treatment of patients with PNS,
  - Review the treatment options for most common PNS:
    - Neurologic syndromes
    - Endocrine syndromes
    - Dermatologic syndromes
    - Rheumatologic syndromes
    - Hematologic/vascular syndromes
  - Summarize the importance of effective treatment of underlying malignant disease and multidisciplinary approach to improve outcomes of patients with PNS.

What are PNS? (1)

- PNS are a group of disorders that can affect patients with malignancy and are **not directly attributalbe to tumor** invasion, tumor compression, metastases or related to treatment.
- PNS are:
  - The result of tumor secretion of hormones or functional peptides (enzymes, growth factors, cytokines) or
  - Related to immune cross-reactivity between tumor and host tissue.
  - For some PNS the mechanisms causing signes and symptoms are still poorly understood.



What are PNS? (2)

- PNS may affect multiple organ systems, most notably:
  - Neurological system (neurological manifestations the most common),
  - Endocrine system,
  - Hematological system,
  - Presents with skin or rheumatologic disorders.
- PNS can an occur **before** (may therfore lead to detection of otherwise clinically occult tumor), **during** or **after** the cancer diagnosis.
- PNS usually appear in later stages of malignant disease and are often associated with poor prognosis.

Epidemiology

- The precise incidence and prevalence of PNS are unknown.
- It is estimated that 10-15% of patients with cancer suffer from a PNS.
- PNS are the second direct cause of death in cancer patients (after cancer itself)
  - About ¼ of cancer patients die of PNS.
- PNS can occur with any malignancy.
  - Small cell lung cancer:
    - The most common cancer associated with PNS.
  - Other neoplasms commonly associated:
    - Breast cancer, ovarian cancer, other adenocarcinomas.
    - lymphoproliferative diseases (especially Hodgkin's disease).
- Males and females are affected equally.
- PNS can be associated also with some benign tumors: e.g. thymoma.

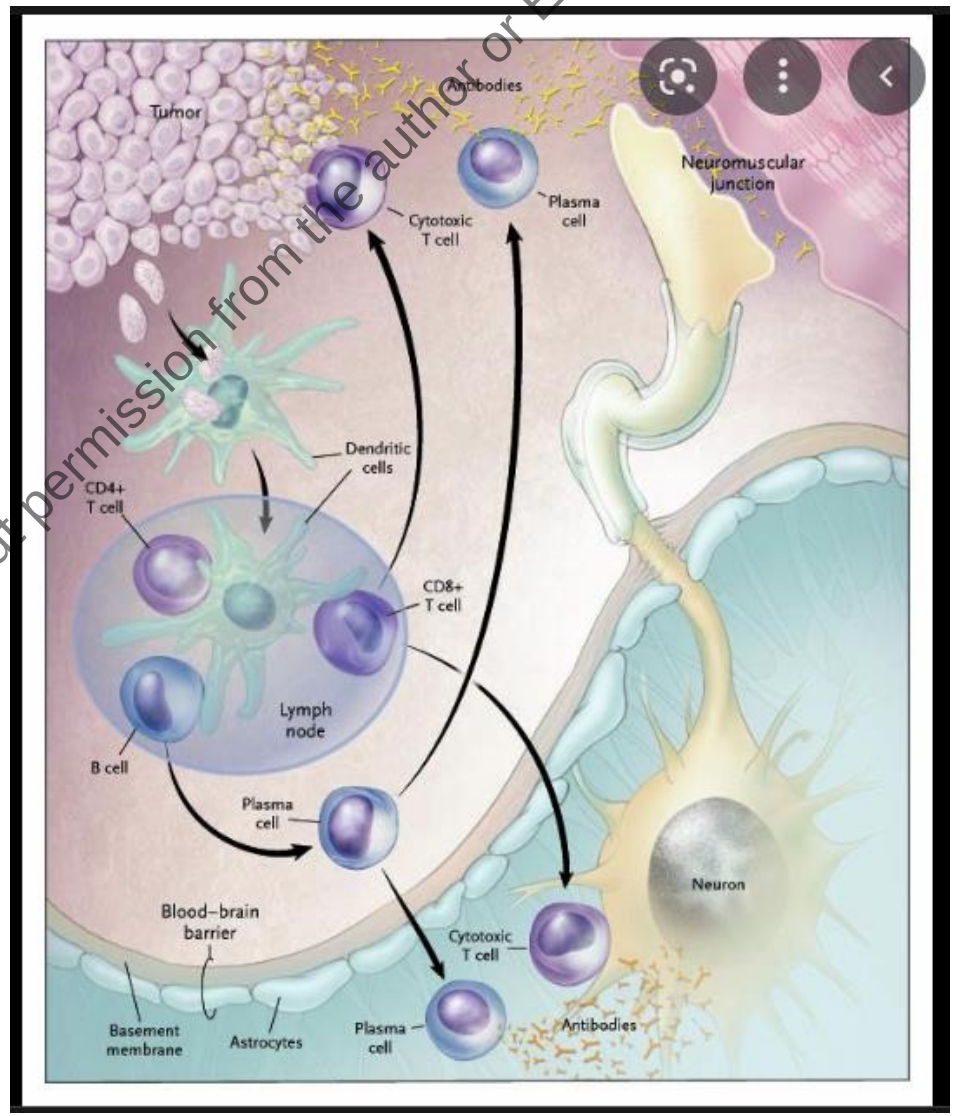
Pathophysiology (1)

Immunologic mechanisms

(more common):

Tumor cc. are immunogenic and lead to the activation of both cell-mediated and humoral immune systems.

- Cytotoxic T cc. recognize antigens on tumor cells, activate themselves. They attack tumor cc. and start generating antibodies against them.
- Normal tissue presents some similar antigens. → The body's immune system can cross-react to them and this lead to symptoms.

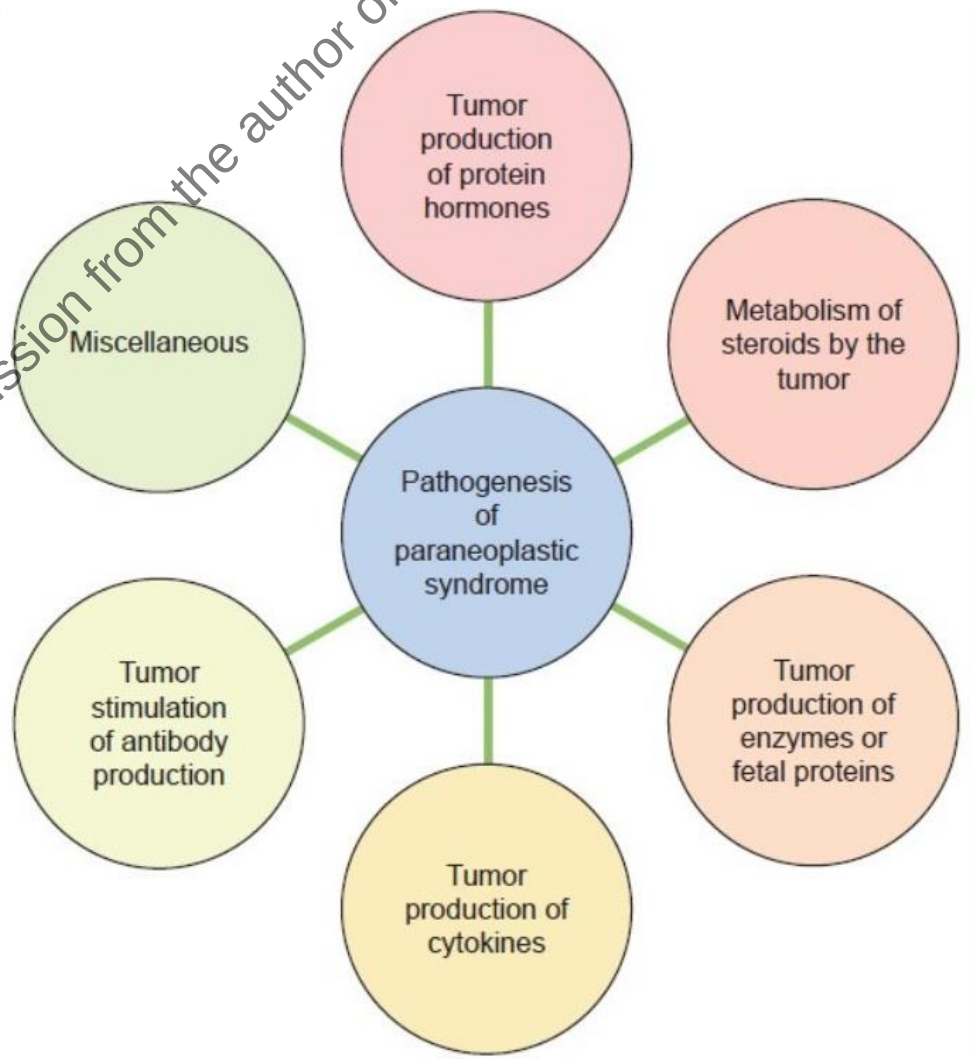


Pathophysiology (2)

Non-immunologic mechanisms:

Tumor cc. produce hormones, functional proteins or cytokines leading to electrolyte and/or metabolic and/or other abnormalities.

- e.g. hyponatremia: excessive secretion of ADH-related peptide,
- e.g. hypercalcemia: excessive secretion of PTH-related peptide.
- Some hematologic malignancies produce immunoglobulins that affect the peripheral nervous system and manifest as peripheral neuropathy.



Diagnosis and clinical presentation

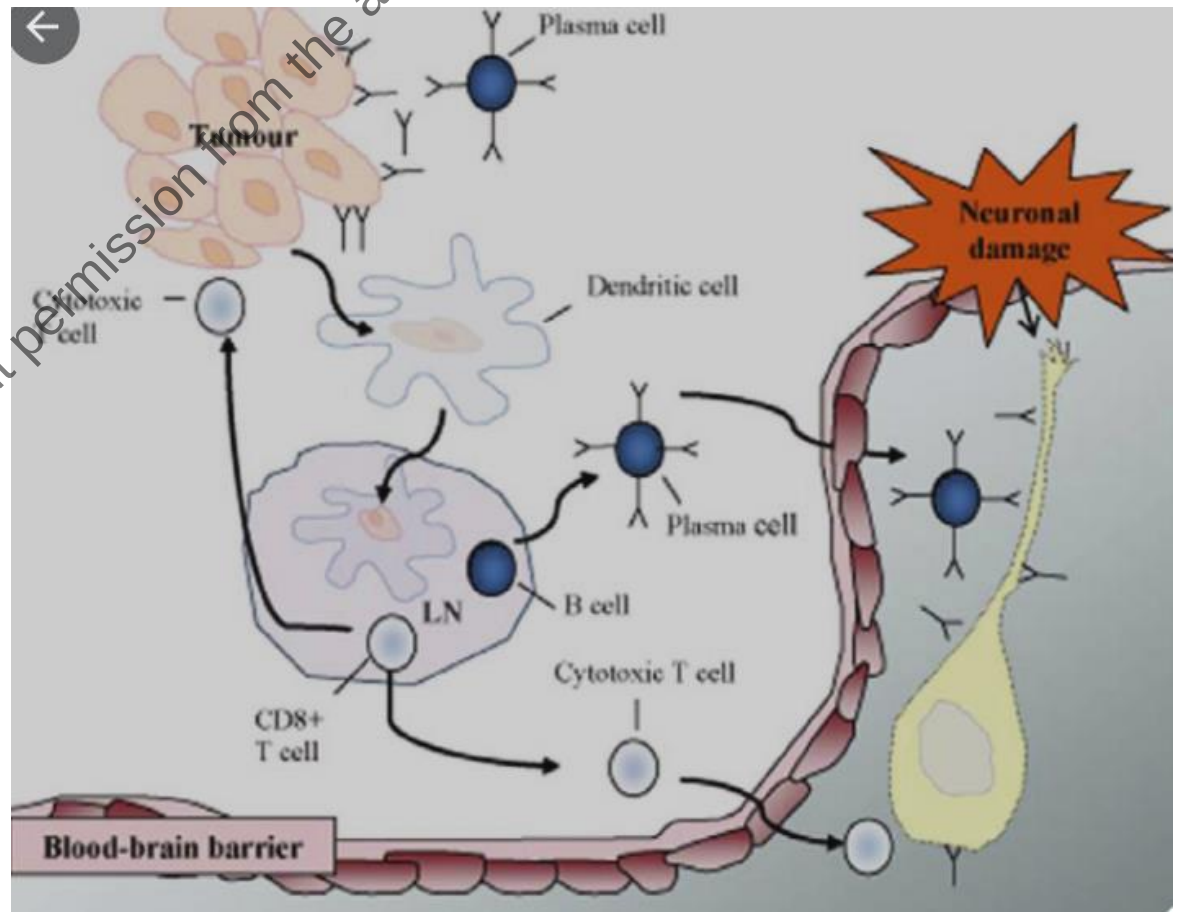
- As PNS can affect multiple organ systems clinical presentations are very heterogeneous and complex.
  - Difficult and challenging in patients with previously unknown (occult) malignant disease.
- Clinical manifestation does not necessarily relate to clinical stage of the underlying malignancy, nor it is related to disease prognosis.
- Most common PNS with clinical presentations, pathophysiology and management according to the affected organ system will be presented.

Paraneoplasitc neurologic syndromes (1)

- Neurologic PNS are heterogenious group of disorders that can affect any part of the nervous system:
  - central nervous system,
  - neuromuscular junction,
  - peripheral nervous system.
- Clinical presentation depends on the level of affected nervous system: cognitive and personal changes, ataxia, cranial nerve deficits, weakness, numbness, etc.
- The diagnosis of neurologic PNS can be challenging as the symptoms may precede the diagnosis of malignant disease.
- Most common associated tumors:
  - Lung cancer (SCLC) (up to 5% of patients), lymphoma (up to 10% of patients), myeloma

Paraneoplasitc neurologic syndromes (2)

- Pathogenesis:
  - Not clearly established: **immune-mediated mechanisms**
  - Immune cross-reactivity between tumor cells and components of nervous system: immune response is targeted against tumor antigens that share some similarities to neuronal antigens, termed **onconeural antigens**.
  - Antibodies (**onconeural antibodies**) and T-cell response against nervous system antigens are a direct cause.
  - Onconeural antibodies may cause permanent damage to the nervous system with substantial morbidity. Early diagnosis is important.



Paraneoplasitc neurologic syndromes (3)

- Diagnostic procedure:
  - Imaging, serologies, EEG, nerve conduction studies, EMG, CSF analysis (to exclude infections)
  - Onconeural antibodies – lack sensitivity and specificity:
    - Up to 30% of patients with PNS do not have detectable antibodies in either serum or CSF.
    - Onconeural antibodies can be detected in some individuals without signs and symptoms of neurologic PNS. Many onconeural antibodies can be detected in patients without cancer.
    - Onconeural antibodies with strong cancer association: anti-CV2, anti-Hu, anti-Ma2, anti-Yo, etc.
- Differential diagnosis is broad:
  - infections, toxins, metabolic disbalance, brain metastases, leptomeningeal disease, adverse effects of treatment
- Treatement:
  - Immune modulators (high dose corticosteroids, rituximab, IV immunoglobulins).
  - Plasmapheresis.
  - Treatment of underlying tumor.
  - If the underlying tumor is successfully treated, subsequent positive antibody titers may indicate tumor relapse.

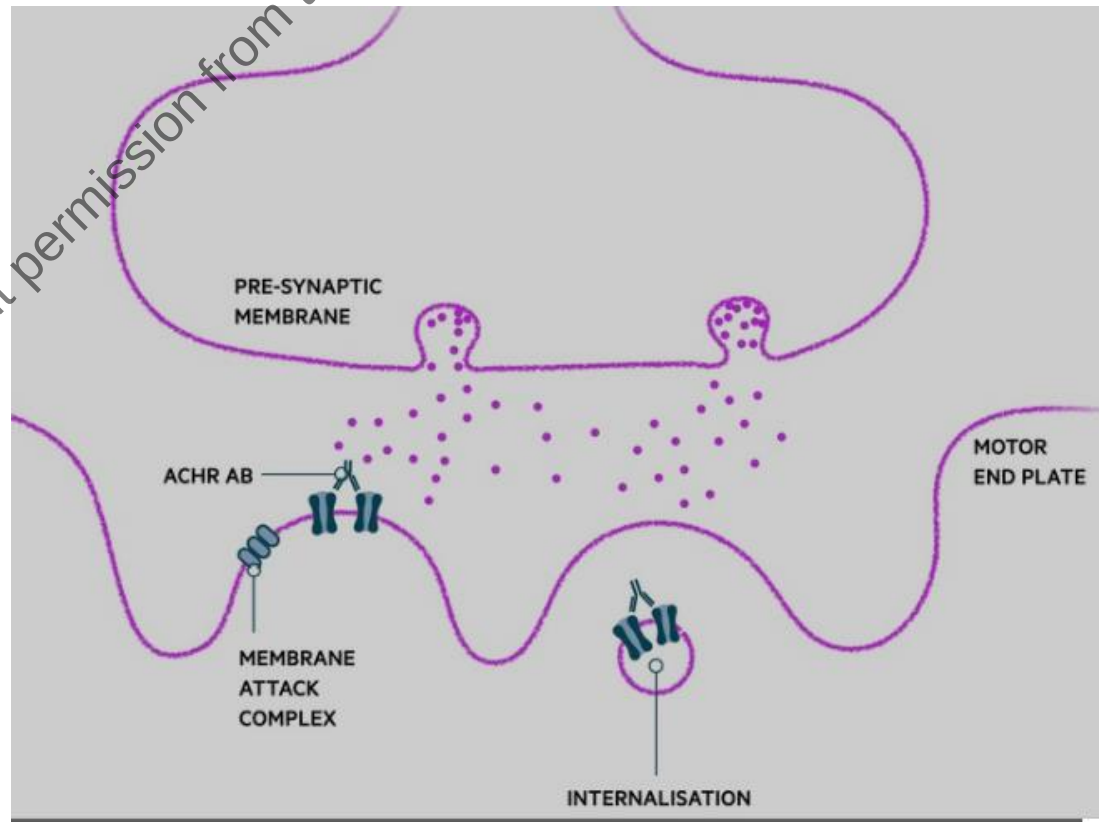
PNS (neurologic): central nervous system (1)

- ***Paraneoplastic Encephalitis/encephalomyelitis:***
  - Patients presentation: cognitive dysfunction, depression, behavior changes, hallucinations, seizures, somnolence, autonomic dysfunction, and less common endocrine dysfunction (if the hypothalamus is involved).
  - Associated onconeural antibodies: anti-Hu, anti-Ma2, anti-CV2
  - Associated cancers: SCLC, testicular germ-cell tumors, breast cancer, Mb.Hodgkin
- ***Subacute cerebellar degeneration:***
  - Patient presentation: ataxia, dysarthria, dysphagia, diplopia, dizziness, nausea, and vomiting.
  - Associated onconeural antibodies: anti-Hu, anti-Yo, , anti-VGCC
  - Associated cancers: SCLC, Mb.Hodgkin, gynecological cancers, breast cancer

PNS (neurologic): neuromuscular junction (1a)

Myasthenia gravis:

- Clinical presentation:
  - Fluctuating weakness of voluntary muscles, ptosis and/or diplopia due to ocular muscle weakness, fatigue, difficulties standing up, climbing stairs, and even swallowing and/or chewing.
  - Muscle weakness worsens throughout the day with increased activity and improves after rest.
- Associated onconeural antibodies:
  - anti-AchR are directed against postsynaptic membrane at the NMJ → impaired neuromuscular transmission.
  - There are also seronegative cases.



anti-AchR - Acetylcholine Receptor Antibody

PNS (neurologic): neuromuscular junction (1b)

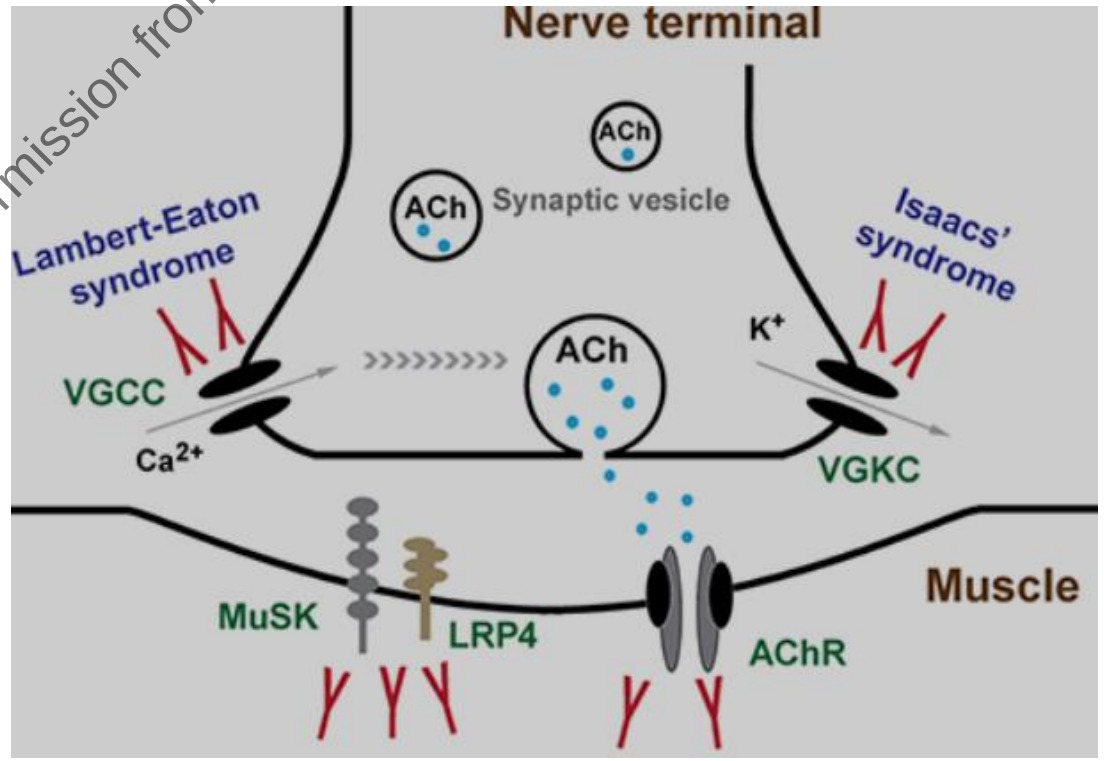
- Associated cancers: thymoma (in 15% of patients), also SCLC, Mb.Hodgkin
- Diagnostic work-up:
  - Clinical examination reveals reduced or absent reflexes, patient's muscle strength improves with repetitive or ongoing use.
  - The blood anti-AchR antibodies are positive.
  - Typical EMG findings - repetitive nerve stimulation results in decremental responses.
- Treatment:
  - Thymectomy.
  - Pyridostigmine (acetylcholinesterase inhibitor) may provide substantial clinical benefit.
  - Corticosteroids, immunomodulators (Cyclosporine A, mycophenolate mofetil), rituximab, IVIG, plasma exchange.
  - Treatment of underlying cancer.

antiAchR – Acetylcholine Receptor Antibody
IVIG - intravenous immunoglobulins

PNS (neurologic): neuromuscular junction (2a)

Lambert-Eaton myasthenic syndrome (LEMS):

- Clinical presentation:
  - weakness of the proximal muscles, predominantly lower extremities (difficulties in basic activities such as climbing stairs, walking, and getting up from a chair), fatigue. Symptoms improve with exercise and throughout the day. In later stages patients also demonstrate autonomic symptoms (dry mouth, decreased sweating, constipation).
- Associated onconeural antibodies:
  - anti-VGCC are directed against presynaptic membrane at the NMJ → decreased ↓ Ca2+ influx → impaired acetylcholine release.



anti-VGCC - Voltage-Gated Calcium Channel Antibody

PNS (neurologic): neuromuscular junction (2b)

- Associated cancers: SCLC (up to 3% of patients), prostate, H&N cancers, lymphomas
- Diagnostic work-up:
  - Clinical examination reveals reduced or absent reflexes, patient's muscle strength improves with repetitive or ongoing use.
  - The blood anti-VGCC antibodies are positive in approximately 85% of patients with LEMS.
  - Typical EMG findings - repetitive nerve stimulation results in incremental responses.
- Treatment:
  - Corticosteroids, IVIG, plasma exchange,
  - 3,4-diaminopyridine (potassium channel blocker) may provide substantial clinical benefit.
  - No response to cholinesterase inhibitors.
  - Treatment of underlying cancer.

antiVGCC – Voltage-Gated Calcium Channels Antibody

PNS (neurologic): peripheral nervous system (1)

- ***Autonomic neuropathy:***
  - Affects parasympathetic, sympathetic, and enteric nervous systems.
  - Clinical presentation:
    - Dry mouth, dry eyes, altered pupillary reflexes, bladder or bowel dysfunction, and orthostatic hypotension.
    - A patient may also manifest as chronic gastrointestinal pseudo-obstruction leading to constipation, nausea, vomiting, dysphagia, and abdominal distension.
  - Associated cancers: SCLC and thymoma.
  - Associated onconeural antibodies: anti-Hu, anti-CV2, anti-amphiphysin
  - Treatment:
    - Symptomatic, corticosteroids.
    - Treatment of underlying cancer.
    - Response to therapy is limited and patient often remain disabled.

PNS (neurologic): peripheral nervous system (2)

- ***Sensory and motor neuropathy:***
  - Clinical presentation:
    - Progressive sensory loss in limbs (glove and stock distribution), even trunk or face, neuropathic pain, decreased sensation, which leads to considerable morbidity
    - Progressive motor weakness, primarily in the lower extremities.
    - Upper and the lower extremities are affected; asymmetric, or symmetric.
    - Considerable morbidity.
  - Associated cancers: SCLC (sensory), lymphomas (motor).
  - Associated onconeural antibodies: anti-Hu, anti-CV2, anti-amphiphysin
  - Differential diagnosis:
    - Broad and challenging: adverse effects of treatment (cytotoxic), metabolic, nutritional, etc.
  - Treatment:
    - Symptomatic, corticosteroids.
    - Treatment of underlying cancer.
    - Response to therapy is limited and patient often remain disabled.

Paraneoplasitc endocrine syndromes

- There are several paraneoplastic syndromes, associated with production and ectopic secretion of different hormones or hormone-like functional proteins:
  - The most common are ectopic excretion of:
    - parathyroid hormone-related peptide (PTHrP)
    - adrenocorticotropic hormone (ACTH),
    - antidiuretic hormone (ADH) by the tumor cells.

PNS (endocrine): Hypercalcemia (1)

- Etiologic factors:
  - Ectopic excretion of PTHrP
    - PTH-rP: a small peptide, the structure and function mimics PHT. It stimulate bone resorption and renal phosphate wasting → hypercalcemia & hypophosphatemia.
  - Ectopic excretion of 1,25 OHD (in particular in lymphomas)
    - 1,25 OHD promotes gastrointestinal absorption of calcium, resulting in suppressed PTH, normal/increased phosphorus and hypercalcemia.
- Common associated tumors:
  - lung cancer, breast cancer, kidney cancer, H&N cancers, multiple myeloma, lymphoma.
- Biochemical presentation:
  - ↑serum calcium, variable serum phosphate, calciuria↓
- Clinical presentation:
  - anorexia, nausea, vomiting, constipation, polydipsia, polyuria, dehydration generalized weakness, acute renal failure, neurologic symptoms: lethargy, altered mental status, hypertonia, cardio-vascular complications: hypertension, life-threatening arrhythmias.

PTHrP - parathyroid hormone-related peptide
1,25 OHD - dihydroxycholecalciferol

PNS (endocrine): Hypercalcemia (2)

- Clinical presentation:
  - Degree of symptoms depends on level of serum calcium, rapidity with which the level was achieved and the patient's overall health
- Differential diagnosis:
  - Hyperparathyroidism (iPTH is generally normal/suppressed in malignancy-related hypercalcemia)
- Treatment:
  - Cardio-vascular stabilization (restoration of intravascular volume), promotion of calciuresis: infusion of normal saline (100-400mL/h)+/- furosemide, in rare cases dialysis may be necessary.
  - Bisphosphonates: the key agents.
  - Calcitonine: has rapid onset of action, can be used in critically ill patients as the effect is not long-term.
  - Corticosteroids: can inhibit calcium resorption, are used mostly in hematologic malignancies (also as a part of specific treatment).
  - Treatment of underlying malignant disease.

iPTH – intact parathyroid hormone

PNS (endocrine): Cushing syndrome (1)

- Etiologic factors:
  - Excessive ACTH
    - Ectopic excretion of ACTH: tumor cells can produce precursor of ACTH (POMC) in large quantities and are capable of converting it to biologically active form.
    - Ectopic production of CRH: which leads to excessive ACTH
- Common associated tumors:
  - lung cancer (SCLC), carcinoid, thyroid cancer (medullary)
- Biochemical presentation:
  - hyperglycemia, hypokalemia, metabolic alkalosis, ↑ ACTH
- Clinical presentation
  - Features associated with Cushing's disease: centripetal obesity, hypertension, muscle weakness, hyperpigmentation, glucose intolerance.

ACTH - adrenocorticotropic hormone
POMC – pro-opiomelanocortin
CRH – corticotropin releasing hormone

PNS (endocrine): Cushing syndrome (2)

- Differential diagnosis:
  - Pituitary and adrenal disorders (↑ ACTH plasma level rules out primary adrenal disease, high-dose dexamethason supression test rules out pituitary related Cushing‘s disesae)
- Treatment:
  - Bilateral adrenalectomy?
  - Drugs that suppress cortisol production: aminoglutethimide, methyrapone, mitotane, ketoconazole
  - Treatment of underlying malignant disease

PNS (endocrine): SIADH (1)

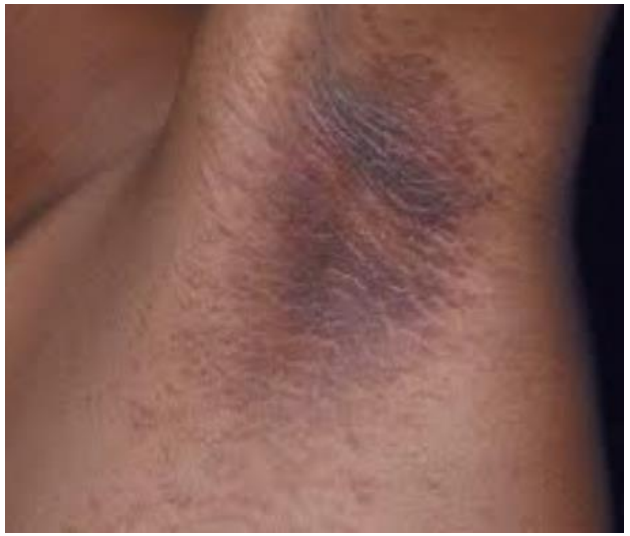
- Etiologic factors:
  - Ectopic/excessive excretion of ADH (vasopressin)
    - It binds to receptors in the renal collecting ducts and Henle loop resulting in increased water reabsorption and increased sodium excretion
- Common associated tumors:
  - lung cancer (SCLC), H&N, brain, GI, prostate, breast cancer, sarcoma, hematologic cancers.
  - In contrast to some other PNS, the presence of SIADH is not related to poor outcome.
- Biochemical presentation:
  - Hyponatremia, euvolemia, low serum osmolality, inappropriately high urine osmolality, ↑ urine sodium, normal renal, adrenal and thyroid function
- Clinical presentation
  - Patient can be asymptomatic, complain of weakness, lethargy, anorexia, headache, may progress to mental status changes, seizures, focal neurological signs and coma.

SIADH – Syndrome of Inappropriate AntiDiuretic Hormone
ADH - AntiDiuretic Hormone

PNS (endocrine): SIADH (2)

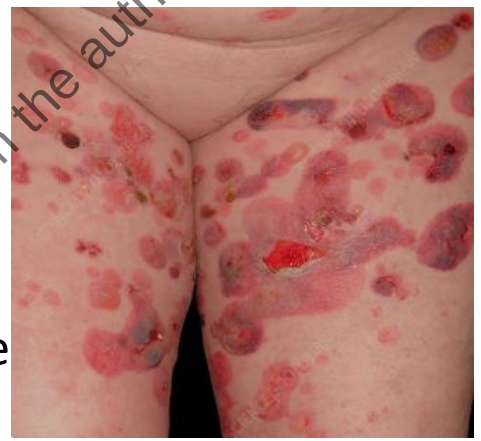
- Differential diagnosis:
  - A number of non-malignant conditions are associated with SIADH:
    - Intracranial processes (infection, vascular disorders, trauma)
    - Pulmonary disease
    - Some drugs: narcotics, carbomazepines, cisplatin, cyclophosphamide
    - Congestive heart failure, renal, liver disease, hypothyroidism, adrenal insufficiency
- Treatment:
  - In mild hyponatremia: fluid restriction
  - In severe situations: 3% hypertonic saline, careful monitoring, ICU (the correction rate should not exceed 1mEq/L/h to avoid the potential complication: pontine demyelinosis)
  - Treatment of underlying malignant disease
- Reappearence of SIADH after treatment competition may herald disease recurrence.

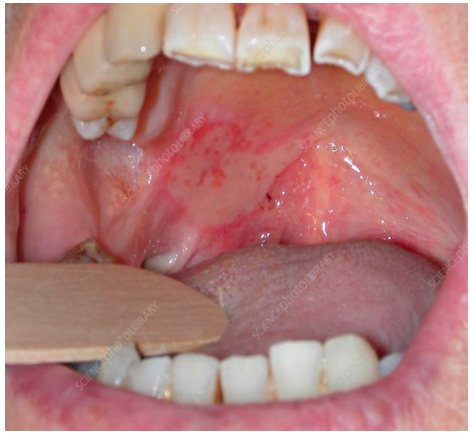
Paraneoplasitc dermatologic syndromes (1)



- ***Acanthosis nigricans:***
  - Clinical presentation:
    - Thickened hyperpigmented skin, usually in the axilla, neck, popliteal and anogenital region. It usually progresses rapidly and diffusely. It can precede the diagnosis of malignant disease.
  - Common associated tumors:
    - Gastric cancer, also lung, breast, ovarian and lymphomas.
  - Differential diagnosis:
    - May be idiopathic or associated with endocrine disorders (diabetes, obesity, polycystic ovary syndrome).
  - Treatment:
    - Treatment of underlying malignant disease.

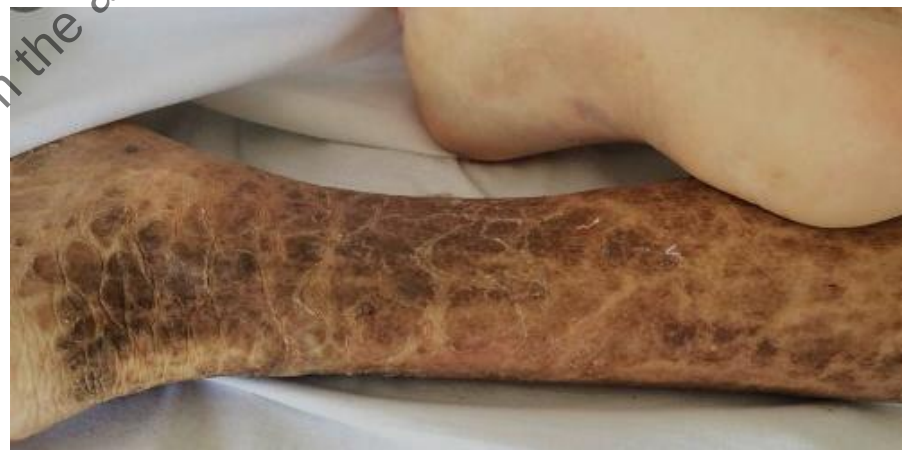
Paraneoplasitc dermatologic syndromes (2)





- ***Paraneoplastic pemphigus:***
  - Clinical presentation:
    - Bullous lesion and erosions over the trunk and the extremities; visceral tissue and mucous membranes can also be effected (painful mucosal erosions)
  - Common associated tumors:
    - B-cell lymphoproliferative diseases.
  - Prognosis:
    - In severe cases it may lead to death due to respiratory failure.
  - Treatment:
    - Corticosteroids, cyclosporine, mycophenolate moetil
    - Treatment of underlying malignant disease.

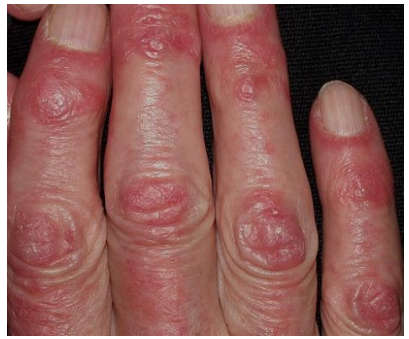
Paraneoplasitc dermatologic syndromes (3)



- ***Ichthyosis:***
  - Clinical presentation:
    - Dry skin with rombiodal scales having free edges involving extensor surfaces of the extremities.
  - Common associated tumors:
    - NHL, lung cancer, breast cancer
  - Associated with some non-malignant situations:
    - Acquired immunodeficiency (AIDS), sarcoidosis, drug induced (cholesterol-lowering agents)
  - Prognosis:
    - Usually follows the diagnosis of cancer and is observed in the late stages of malignant disease.
  - Treatment:
    - Treatment of underlying malignant disease.

Paraneoplasitc dermatologic syndromes (4)

- ***Dermatomyositis:***
  - Clinical presentation:
    - Inflammatory myopathy with skin changes, characterized with heliotrope rash on the upper eyelids, an erythematous rash on the face, neck, back, chest, and shoulders and eruptions on phalangeal joints, and. Beside these, patients can present with inflammatory myopathies with proximal muscle weakness and muscle tenderness.
  - Diagnostic findings:
    - Lab. findings: Elevated serum CK, AST, ALT, LDH and aldolase
    - EMG: increased spontaneous activity with fibrillations
    - Biopsy: perivascular inflammatory infiltrate, muscle fibre atrophy
  - Common associated tumors:
    - Ovarian, breast, lung, prostate, H&N cancers, NHL
  - Prognosis:
    - Depends mainly on prognosis of malignant disease.
  - Treatment:
    - Corticosteroids, cyclosporine, mycophenolate moetil
    - Treatment of underlying malignant disease.



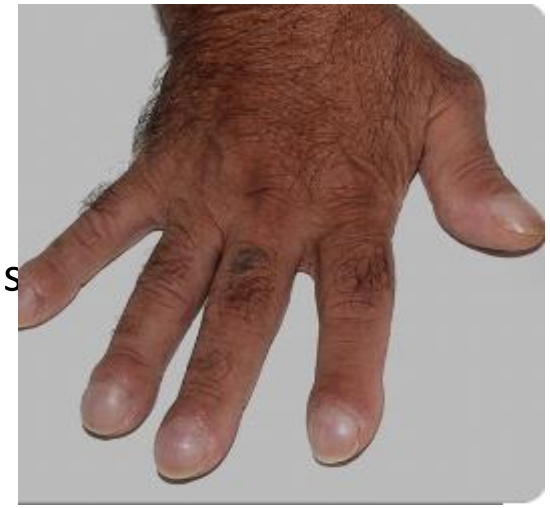
CK – Creatine Kinase

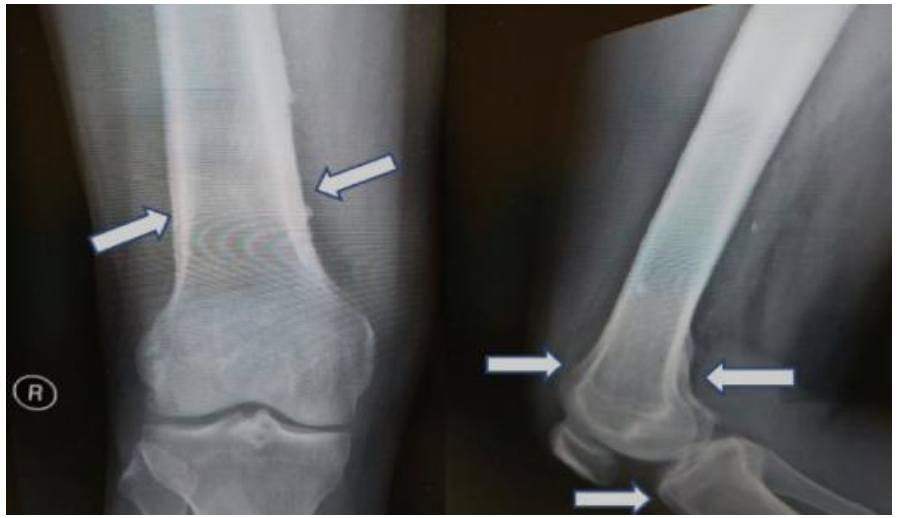
Paraneoplasitc rheumatologic syndromes (1)

- ***Paraneoplastic polyarthritis:***
  - Clinical presentation:
    - Commonly involves large joints and is characterized by migratory, non-erosive, asymmetric polyarthritis → significant morbidity.
    - Is usually seronegative.
  - Common associated tumors: lung, breast, ovarian, pancreatic cancer, lymphomas.
  - Treatment: Treatment of underlying cancer, NSAIDs.

Paraneoplasitc rheumatologic syndromes (2)

- ***Hypertrophic osteoarthropathy (HOA):***
  - The most known cancer associated arthropathy.
  - Etiology:
    - ectopic VEGF and/or PDGF and/or prostaglandin E2→ increased angiogenesis
    - Fibroblast/osteoblast activity → connective tissue and bone synthesis.
  - Clinical presentation: finger clubbing
  (paronychial soft tissue expansion) and periostitis (tibia, femur)
  → significant morbidity.
  - Differential diagnosis: secondary HOA
  (right to left shunting: cardiac, pulmonary, liver disease).
  - Common associated tumors:
    - Lung and esophageal cancer, thymoma.
  - Treatment:
    - Treatment of underlying cancer, NSAIDs.





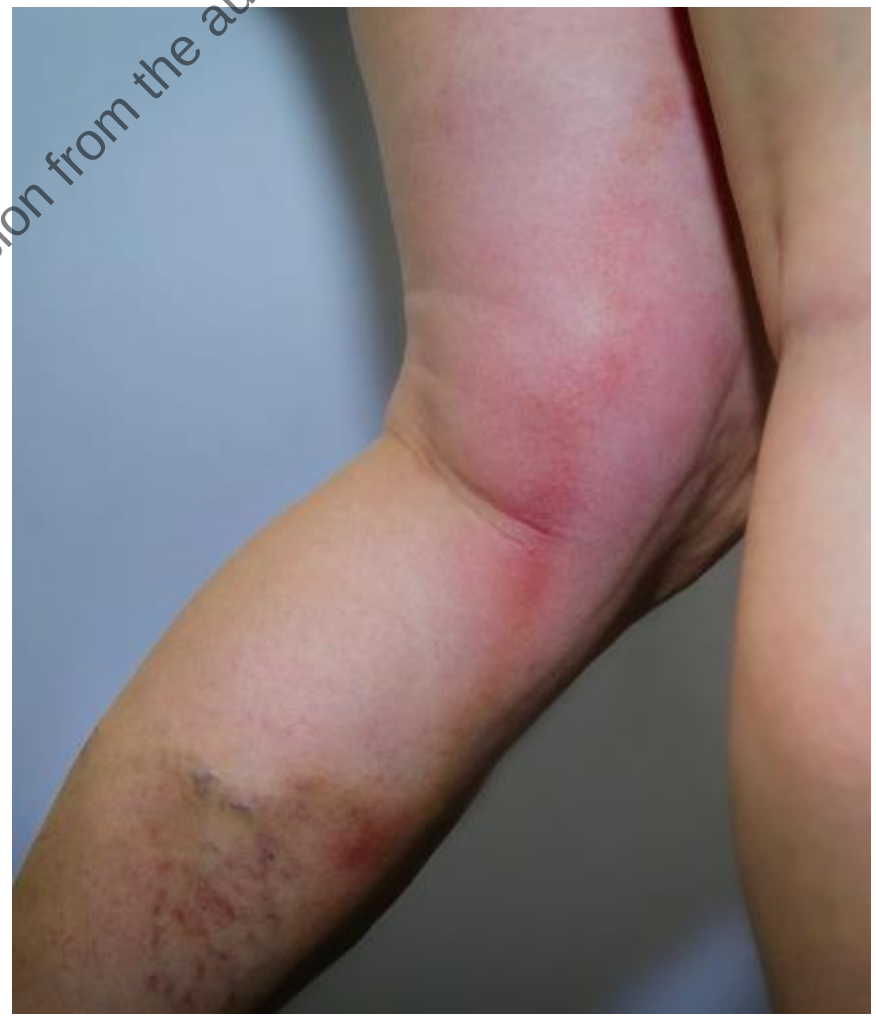
VEGF – Vascular Endothelial Growth Factor
PDGF - Platelet-derived growth factor

Paraneoplasitc rheumatologic syndromes (3)

- Several ***non-articular paraneoplastic rheumatic syndromes***:
  - Various types of vasculitis
  - Various types of inflammatory muscle conditions
  - Lupus-like syndrome
  - Raynaud's phenomenon
- In general they improve/subside with effective cancer treatment.

Paraneoplastic coagulation disorders (1)

- ***Thrombophlebitis/Trousseau's syndrome***
  - Malignancy-related hypercoagulability → recurring clots that resolve and appear again elsewhere in the body (present also at some unusual sites).
  - Etiology: most probably complex
    - Release of procoagulant agents (e.g. cytokines) from tumor vessels or tumor cells
    - Platelet hyperactivity
  - Clinical presentation: Pain, tenderness, induration, and erythema overlying the affected vessel.
  - Common associated tumors: lung, pancreatic, breast, ovarian cancer.
  - Treatment: treatment is rarely effective if the underlying malignancy is not treated as the syndrome is often heparin and warfarin resistant.



Paraneoplastic coagulation disorders (2)

- ***Disseminated intravascular coagulation (DIC)***
  - A condition with over-consumption of platelets and clotting factors → hemorrhage and/or thrombosis (life- threatening complications: thrombotic endocarditis, emboli to the brain, etc.)
  - Common associated tumors: a number of solid tumors, aggressive leukemia
  - Treatment:
    - Supportive treatment (heparin, platelets, fresh frozen plasma).
    - Treatment of underlying cancer.

Other PNS

- ***Neoplastic fever***
  - Clinical presentation: fever, general malaise, weight loss
  - Etiology: likely cytokine-mediated (pyrogen cytokines produced by tumor cells – IL-1, TNF, IL-6, etc.)
  - Common associated tumors: most cancers, in particular hematologic malignancies
  - Treatment: NSAIDs, corticosteroids, treatment of underlying cancer.
- ***Cancer cachexia***
  - Clinical presentation: anorexia, altered taste, food aversion, weight loss, weakness, decline in performance status
  - Etiology:
    - Not fully understood, multifactorial – a number of cytokines, functional proteins have been implicated as putative agents (metabolic abnormalities adapted to nutritional needs of the tumor over the host)
  - Common associated tumors: most cancers
  - Treatment: challenging – megestrol acetate, cannabiol derivates, EPA
    - Clear benefit of any type of nutritional support has not been demonstrated to date.
    - Treatment of underlying cancer.

EPA – eicosapentaenoic acid

Prognosis

- PNS have diverse pathophysiological mechanisms, diverse clinical manifestations, and hence diverse prognosis.
- The key therapy is effective treatment of underlying malignancy.
- As PNS are usually associated with more advanced malignant disease stage the prognosis of patients with PNS is usually poor.
- Death may result from the underlying progression of cancer, from complications of cancer treatments, or an irreversible multiple organ system impairment, indirectly associated with PNS:
  - e.g. acute respiratory failure, congestive heart failure, kidney failure, etc.

Conclusions

- PNS are rare clinical syndromes due to systemic effects of tumors.
- The two main causes are:
  - Tumor secretions of hormones, functionally active peptides or cytokines
  - Immunological mechanisms with cross-reacting antibodies between tumor and normal tissues.
- Different organs and systems can be affected with diverse clinical presentation.
- PNS could be the first manifestation of malignant disease.
- PNS are often a diagnostic and therapeutic chellange. Because of the complex diagnostic work-up, the condition is best managed by a MDT.
- Outcome of the patients with PNS mainly depend on efficacy of treatment of underlying malignant disease.

Relevant literature

- Govinda, R., Stinchcombe , T.E. et al. Paraneoplastic Syndromes. Paraneoplastic Syndromes. In: Cancer. Principles & Practice of Oncology. Wolters Kluwer Health, ISBN 978-1-4511-9294-0.
- Gadgeel, S.M., Wozniak, A.J., et al. (2006). Paraneoplastic Syndromes. In: Oncology. Springer, New York, NY. https://doi.org/10.1007/0-387-31056-8_85
- Pelosof LC, Gerber DE. Paraneoplastic syndromes: an approach to diagnosis and treatment. Mayo Clin Proc. 2010 Sep;85(9):838-54. doi: 10.4065/mcp.2010.0099. Erratum in: Mayo Clin Proc. 2011 Apr;86(4):364. Dosage error in article text. PMID: 20810794; PMCID: PMC2931619.
- Sardiña González C, Martínez Vivero C, López Castro J. Paraneoplastic syndromes review: The great forgotten ones. Crit Rev Oncol Hematol. 2022 Jun;174:103676. doi: 10.1016/j.critrevonc.2022.103676. Epub 2022 Apr 2. PMID: 35378267.
- Henry K. Paraneoplastic syndromes: Definitions, classification, pathophysiology and principles of treatment. Semin Diagn Pathol. 2019 Jul;36(4):204-210. doi: 10.1053/j.semdp.2019.01.002. Epub 2019 Feb 1. PMID: 30876820.