ΠΑΡΑΝΕΟΠΛΑΣΜΑΤΙΚΑ ΣΥΝΔΡΟΜΑ

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ΠΓΝΑ ΑΤΤΙΚΟΝ

Ορισμός

- Ο όρος **παρανεοπλασματικό σύνδρομο** αντιστοιχεί σε ομάδα παθολογικών καταστάσεων που χαρακτηρίζεται από ποικιλία κλινικών εκδηλώσεων, παρατηρούνται σε ασθενείς που πάσχουν από κακόηθες νεόπλασμα, αλλά η εκδήλωσή τους δεν σχετίζεται με την ανατομική παρουσία του νεοπλάσματος η μεταστάσεων του

Επιδημιολογία

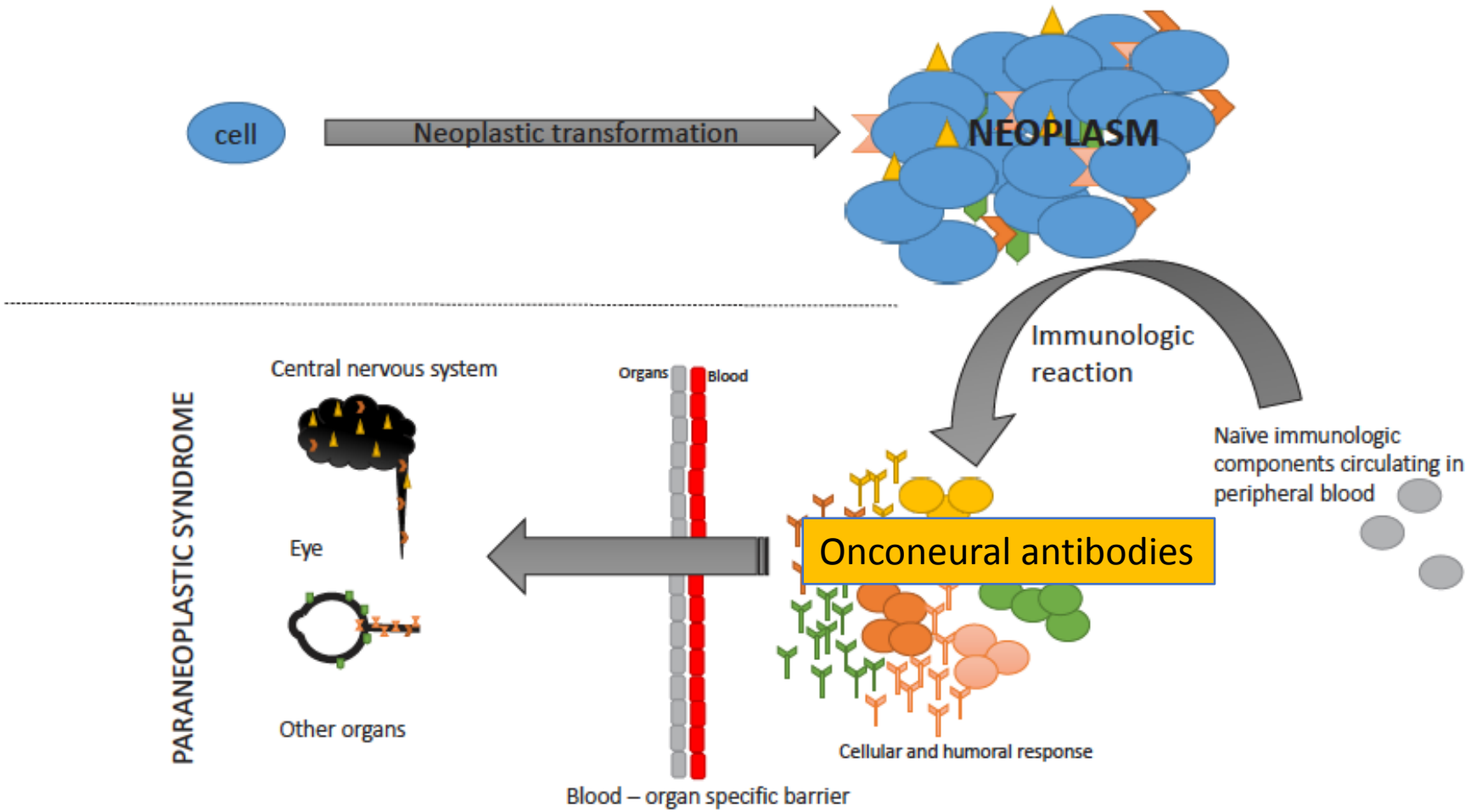
- Εκτιμάται ότι 7–15% ασθενείς με κακοήθη νόσο παρουσιάζουν κάποιο παρανεοπλασματικό σύνδρομο.
- Η συχνότητα ποικίλλει ανάλογα με τον τύπο του καρκίνου και το στάδιο της νόσου
- Μπορεί να εμφανισθούν ΠΡΙΝ η ΜΕΤΑ την διάγνωση της νεοπλασίας
- Πιο συχνά σε: καρκίνο πνεύμονα, καρκίνο μαστού, αιματολογικές κακοήθειες, γυναικολογικοί καρκίνοι, καρκίνος προστάτου

Παθοφυσιολογικός Μηχανισμός (1)

- Ο όγκος διαθέτει η δημιουργεί αντιγόνα, κυτταροκίνες, ορμόνες η πεπτίδια
- Οι ουσίες αυτές μπορούν να επηρεάσουν δυνητικά οποιοδήποτε σύστημα παράγοντας τα αντίστοιχα συμπτώματα (νευρολογικά, δερματολογικά, ΓΕΣ, ενδοκρινικά, μεταβολικά, καρδιαγγειακά κλπ) μέσω ανοσολογικών η μη ανοσολογικών μηχανισμών

Ανοσολογικός Μηχανισμός

(*νευρολογικά, ρευματολογικά, δερματολογικά παρανεοπλασματικά σύνδρομα*)



Ανοσολογικός μηχανισμός

- 80% εμφανίζονται ΠΡΙΝ την διάγνωση του καρκίνου
- Συχνά δεν υποχωρούν με την αντιμετώπιση της νεοπλασίας

Μη ανοσολογικός Μηχανισμός *(ενδοκρινολογικά παρανεοπλασματικά σύνδρομα)*

- Υπερασβεστιαιμία
- Υπερέκκριση αντιδιουρητικής ορμόνης
- Παραγωγή ανοσοσφαιρινών από αιματολογικές κακοήθειες, οι οποίες δημιουργούν βλάβες στον νευρικό ιστό.

Μη ανοσολογικός μηχανισμός

- Εμφανίζονται ΜΕΤΑ την διάγνωση του καρκίνου
- Κατά κανόνα υποχωρούν με την αντιμετώπιση της νεοπλασίας

Διάγνωση

- Εξ αποκλεισμού
- Αυτοαντισώματα

Ταξινόμηση

- Ανάλογα με το σύστημα που επηρεάζουν
- Ανάλογα με το νεόπλασμα που τα προκαλεί

Ταξινόμηση

- Ανάλογα με το σύστημα που επηρεάζουν
- Ανάλογα με το νεόπλασμα που τα προκαλεί

Νευρικό σύστημα (1)

Syndrome	Clinical presentation	Associated antibodies[b]	Diagnostic studies	Associated cancers
Limbic encephalitis (LE)	Mood changes, hallucinations, memory loss, seizures, and less commonly hypothalamic symptoms (hyperthermia, somnolence, endocrine dysfunction); onset over days to months	anti-Hu (typically with small cell lung cancer) anti-Ma2 (typically testicular cancer) anti-CRMP5 (anti-CV2) anti-amphiphysin	EEG: epileptic foci in temporal lobe(s); focal or generalized slow activity FDG-PET: increased metabolism in temporal lobe(ss) MRI: hyperintensity in medial temporal lobe(s) CSF analysis: pleocytosis, elevated protein, elevated IgG, oligoclonal bands	SCLC (~40%-50% of LE patients), testicular germ-cell (~20% of LE patients), breast (~8% of LE patients), thymoma, teratoma, Hodgkin lymphoma
Paraneoplastic cerebellar degeneration	Ataxia, diplopia, dysphagia, dysarthria; prodrome of dizziness, nausea, vomiting	anti-Yo anti-Hu anti-CRMP5 (anti-CV2) anti-Ma anti-Tr anti-Ri anti-VGCC anti-mGluR1	FDG-PET: increased metabolism (early stage) and then decreased metabolism (late stage) in cerebellum MRI: cerebellar atrophy (late stage)	SCLC, gynecologic, Hodgkin lymphoma, breast
Lambert-Eaton myasthenia syndrome (LEMS)	Lower extremity proximal muscle weakness, fatigue, diaphragmatic weakness, bulbar symptoms (usually milder than in MG); later in course, autonomic symptoms (ptosis, impotence, dry mouth) in most patients	anti-VGCC (P/Q type)	EMG: low compound muscle action potential amplitude; decremental response with low-rate stimulation but incremental response with high-rate stimulation	SCLC (~3% of patients have LEMS), prostate, cervical, lymphomas, adenocarcinomas

Νευρικό σύστημα (2)

Syndrome	Clinical presentation	Associated antibodies[b]	Diagnostic studies	Associated cancers
Myasthenia gravis (MG)	Fatigable weakness of voluntary muscles (ocular-bulbar and limbs), diaphragmatic weakness	anti-AchR	EMG: decremental response to repetitive nerve stimulation	Thymoma (in ~15% of MG patients)
Autonomic neuropathy	Panautonomic neuropathy, often subacute onset (weeks), involving sympathetic, parasympathetic, and enteric systems; orthostatic hypotension; GI dysfunction; dry eyes/mouth; bowel/bladder dysfunction; altered pupillary light reflexes; loss of sinus arrhythmia CGP: constipation, nausea/vomiting, dysphagia, weight loss, abdominal distention	anti-Hu anti-CRMP5 (anti-CV2) anti-nAchR anti-amphiphysin	Abdominal radiography/barium studies/CT: GI dilatation but no mechanical obstruction (for CGP) Esophageal manometry: achalasia or spasms (for CGP)	SCLC, thymoma
Subacute (peripheral) sensory neuropathy	Parasthesias/pain (typically upper extremities before lower), followed by ataxia; multifocal/asymmetric distribution; all sensory modalities decreased but especially deep sensation/pseudoathetosis of hands; deep tendon reflexes decreased/absent; onset over weeks to months	anti-Hu anti-CRMP5 (anti-CV2) anti-amphiphysin	NCS: reduced/absent sensory nerve action potentials CSF analysis: pleocytosis, high IgG, oligoclonal bands	Lung (~70%-80%), usually SCLC; breast, ovarian; sarcomas; Hodgkin lymphoma

Διάγνωση (1)

Βέβαια

- **Τυπικό νευρολογικό σύνδρομο*** και κακοήθεια που αναπτύσσεται εντός 5ετίας από την εμφάνιση της νευρολογικής συνδρομής

  *Εγκεφαλομυελίτιδα, limbic encephalitis, υποξεία παρεγκεφαλιδική ατροφία, σύνδρομο οψόκλονου-μυοκλονίας, μυασθενικό σύνδρομο Lambert Eaton, υποξεία αισθητική νευροπάθεια, χρόνια ψευδοαπόφραξη ΓΕΣ, δερματομυοσίτιδα.

- **Μη τυπικό σύνδρομο** που
  - βελτιώνεται σημαντικά με την θεραπεία της υποκείμενης νεοπλασίας και το οποίο δεν χαρακτηρίζεται από αυτόματη υποχώρηση.
  - Συνδέεται με την ύπαρξη παρανεοπλασματικών αντισωμάτων και ανάπτυξη κακοήθειας εντός 5ετίας από την εμφάνιση της νευρολογικής συνδρομής.

- **Τυπικό η μη τυπικό σύνδρομο** που χαρακτηρίζεται από «τυπικά» παρανεοπλασματικά αντισώματα*.

  *anti-Hu, Yo, Ri, CV2/CRMP-5, Ma2, and amphiphysin.

Διάγνωση (1)

Πιθανή

- **Τυπικό νευρολογικό σύνδρομο** χωρίς παρανεοπλασματικά αντισώματα και καρκίνο, αλλά με υψηλό κίνδυνο ανάπτυξης κακοήθειας

- **Μη τυπικό σύνδρομο** χωρίς παρανεοπλασματικά αντισώματα, αλλά ανάπτυξη κακοήθειας εντός 2ετίας από την εμφάνιση της νευρολογικής συνδρομής.

- **Τυπικό η μη τυπικό σύνδρομο** με «μη τυπικά» παρανεοπλασματικά αντισώματα και χωρίς ανάπτυξη κακοήθειας εντός 2ετίας από την εμφάνιση της νευρολογικής συνδρομής.

Ενδοκρινείς αδένες

TABLE 1. **Paraneoplastic Endocrine Syndromes**[a,b]

Syndrome	Clinical presentation	Laboratory findings	Associated cancers	Treatment options[c]	References
SIADH	Gait disturbances, falls, headache, nausea, fatigue, muscle cramps, anorexia, confusion, lethargy, seizures, respiratory depression, coma	Hyponatremia: mild, sodium 130-134 mEq/L; moderate, sodium, 125-129 mEq/L; severe, sodium <125 mEq/L Increased urine osmolality (>100 mOsm/kg in the context of euvolemic hyponatremia)	Small cell lung cancer, mesothelioma, bladder, ureteral, endometrial, prostate, oropharyngeal, thymoma, lymphoma, Ewing sarcoma, brain, GI, breast, adrenal	Restrict fluids (usually <1000 mL/d) and encourage adequate salt and protein intake Demeclocycline, 300-600 mg orally twice daily Conivaptan, 20-40 mg/d IV Tolvaptan, ~10-60 mg/d orally Hypertonic (3%) saline at <1-2 mL/kg/h	5-7
Hyper-calcemia	Altered mental status, weakness, ataxia, lethargy, hypertonia, renal failure, nausea/vomiting, hypertension, bradycardia	Hypercalcemia: mild, calcium 10.5-11.9 mg/dL; moderate, calcium 12.0-13.9 mg/dL; severe, calcium ≥14.0 mg/dL Low to normal (<20 pg/mL) PTH level Elevated PTHrP level	Breast, multiple myeloma, renal cell, squamous cell cancers (especially lung), lymphoma (including HTLV-associated lymphoma), ovarian, endometrial	Normal saline, 200-500 mL/h Furosemide, 20-40 mg IV (use with caution and only after adequate fluid resuscitation) Pamidronate, 60-90 mg IV Zoledronate, 4 mg IV Prednisone, 40-100 mg/d orally (for lymphoma, myeloma) Calcitonin, 4-8 IU/kg SC or IM every 12 h Mithramycin, 25 μg/kg IV (often requires multiple doses) Gallium nitrate, 100-200 mg/m^2/d IV continuous infusion for 5 d Hemodialysis	4, 8, 9
Cushing syndrome	Muscle weakness, peripheral edema, hypertension, weight gain, centripetal fat distribution	Hypokalemia (usually <3.0 mmol/L), elevated baseline serum cortisol (>29.0 μg/dL), normal to elevated midnight serum ACTH (>100 ng/L) not suppressed with dexamethasone	Small cell lung cancer, bronchial carcinoid (neuroendocrine lung tumors account for ~50%-60% of cases of paraneoplastic Cushing syndrome), thymoma, medullary thyroid cancer, GI, pancreatic, adrenal, ovarian	Ketoconazole, 600-1200 mg/d orally Octreotide, 600-1500 μg/d SC or octreotide LAR, 20-30 mg IM monthly Aminoglutethimide, 0.5-2 g/d orally Metyrapone, ~1.0 g/d orally Mitotane, 0.5-8 g/d orally Etomidate, 0.3 mg/kg/h IV Mifepristone, 10-20 mg/kg/d orally Adrenalectomy	10-14
Hypo-glycemia	Sweating, anxiety, tremors, palpitations, hunger, weakness, seizures, confusion, coma	For non–islet cell tumor hypoglycemia: low glucose, low insulin (often <1.44-3.60 μIU/mL), low C-peptide (often <0.3 ng/mL), elevated IGF-2:IGF-1 ratio (often >10:1) For insulinomas: low glucose, elevated insulin, elevated C-peptide, normal IGF-2:IGF-1 ratio	Mesothelioma, sarcomas, lung, GI	Glucose (oral and/or parenteral) Dexamethasone, 4 mg 2 or 3 times daily Prednisone, 10-15 mg/d Diazoxide, 3-8 mg/kg/d orally divided in 2 or 3 doses Glucagon infusion, 0.06-0.3 mg/h IV Octreotide, ~50-1500 μg/d SC or octreotide LAR, 20-30 mg IM monthly (often with corticosteroids) Human growth hormone, 2 U/d SC (often with corticosteroids)	4, 15-20

[a] ACTH = adrenocorticotropic hormone; GI = gastrointestinal; HTLV = human T-lymphotropic virus; IM = intramuscular; IV = intravenous; LAR = long-acting release; PTH = parathyroid hormone; PTHrP = PTH-related protein; SC = subcutaneous; SIADH = syndrome of inappropriate antidiuretic hormone secretion. See Glossary at end of article for expansion of additional abbreviations.

[b] SI conversion factors: To convert calcium values to mmol/L, multiply by 0.25; to convert cortisol values to nmol/L, multiply by 27.588; to convert C-peptide values to nmol/L, multiply by 0.331; to convert insulin values to pmol/L, multiply by 6.945; to convert osmolality values to mmol/kg, multiply by 1; to convert PTH values to ng/L, multiply by 1; and to convert sodium values to mmol/L, multiply by 1.

[c] In addition to treating the underlying malignancy.

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SIADH			

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Hyper-
calcemia

Hyper-calcemia	Altered mental status, weakness, ataxia, lethargy, hypertonia, renal failure, nausea/vomiting, hypertension, bradycardia	

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Cushing syndrome

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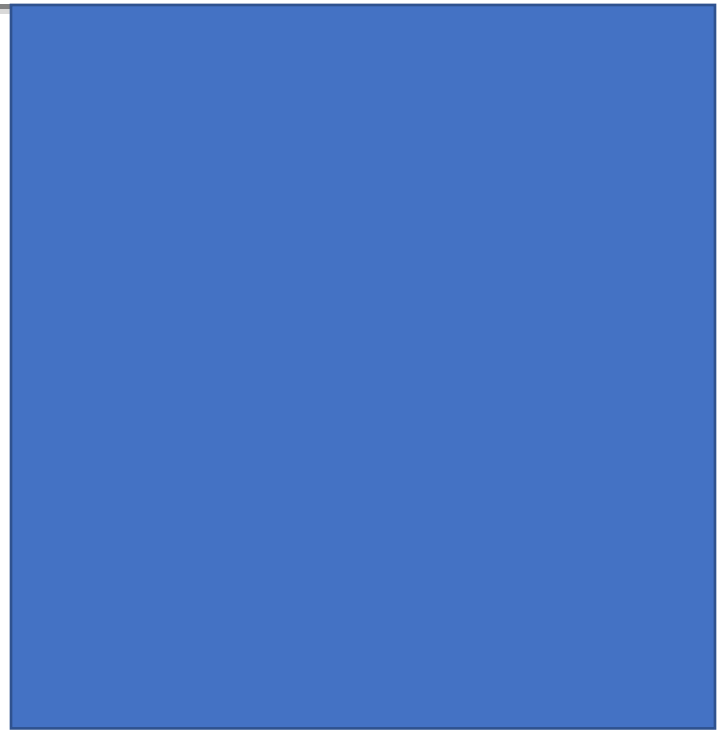

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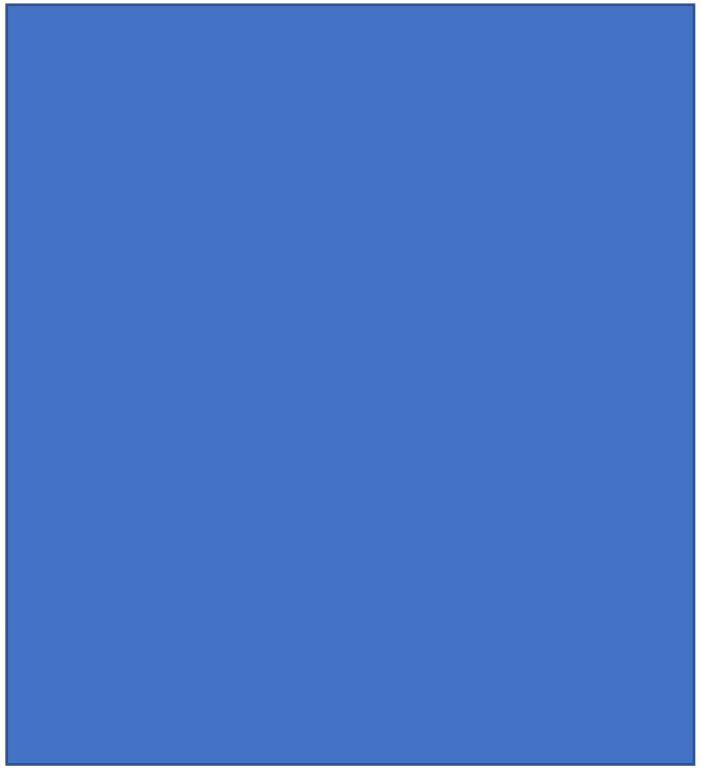
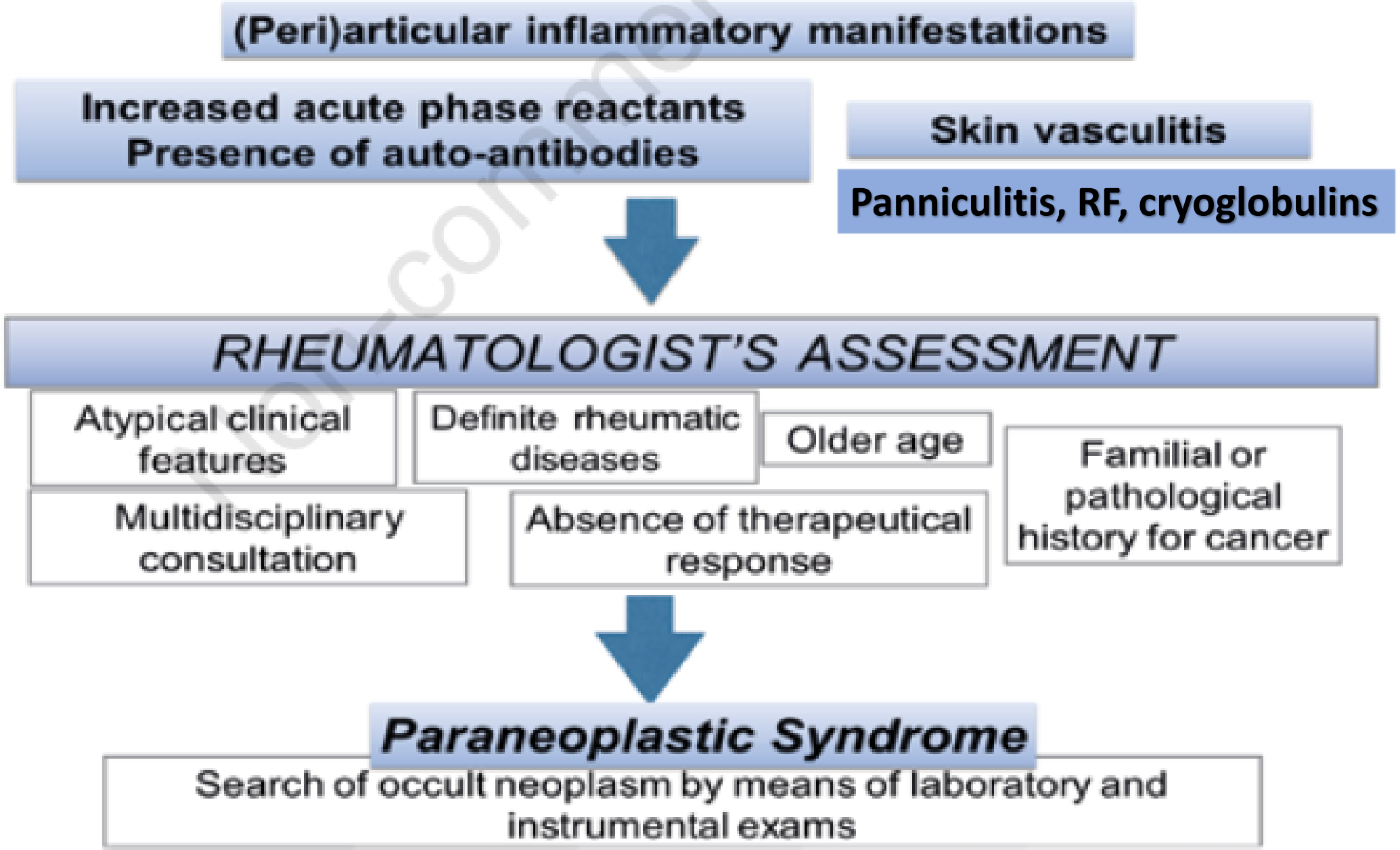
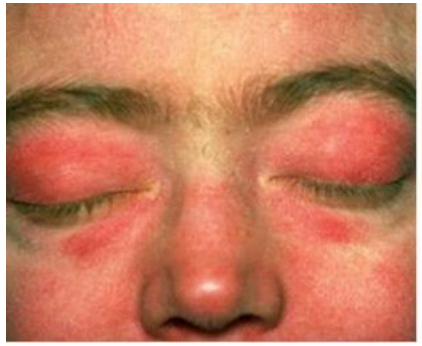


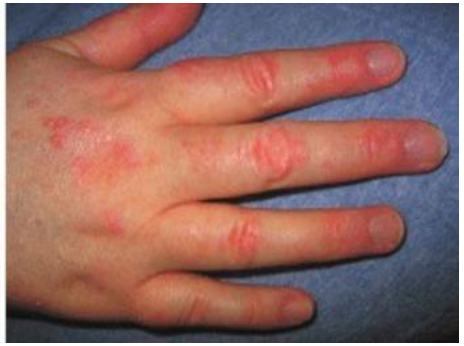
Hypo-glycemia	Sweating, anxiety, tremors, palpitations, hunger, weakness, seizures, confusion, coma	For non–islet cell tumor hypoglycemia: low glucose, low insulin (often <1.44-3.60 μIU/mL), low C-peptide (often <0.3 ng/mL), elevated IGF-2:IGF-1 ratio (often >10:1) For insulinomas: low glucose, elevated insulin, elevated C-peptide, normal IGF-2:IGF-1 ratio	Mesothelioma, sarcomas, lung, GI

Συνδετικός ιστός

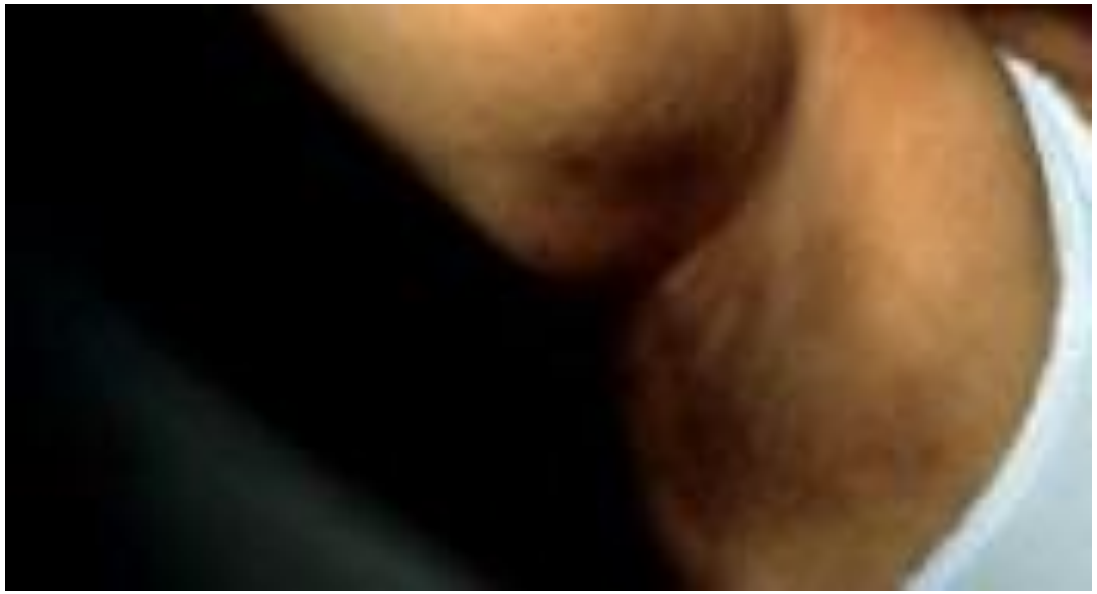
Inflammatory joint and tendon-muscle diseases	Hypertrophic osteoarthropathy Relapsing polychondritis Secondary gout Jaccoud's arthropathy Amyloid arthropathy Multicentric reticulohistiocytosis Carcinomatous polyarthritis Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) Adult onset Still's disease Palmar fasciitis and polyarthritis Eosinophilic fasciitis Localized nodular myositis
Vasculitis	Leukocytoclastic vasculitis Polyarteritis nodosa Granulomatous polyangiitis Eosinophilic granulomatosis with polyangiitis Microscopic necrotizing polyangiitis Horton's giant cell arteritis Polymyalgia rheumatica Cryoglobulinemia Erythema nodosum
Connective tissue diseases	Dermatomyositis/Polymyositis Systemic sclerosis Systemic lupus erythematosus Paraneoplastic acral vascular syndrome


(Peri)articular inflammatory manifestations
Increased acute phase reactants
Presence of auto-antibodies
Skin vasculitis
Panniculitis, RF, cryoglobulins
RHEUMATOLOGIST'S ASSESSMENT
Atypical clinical features
Definite rheumatic diseases
Older age
Familial or pathological history for cancer
Multidisciplinary consultation
Absence of therapeutical response
Paraneoplastic Syndrome
Search of occult neoplasm by means of laboratory and instrumental exams

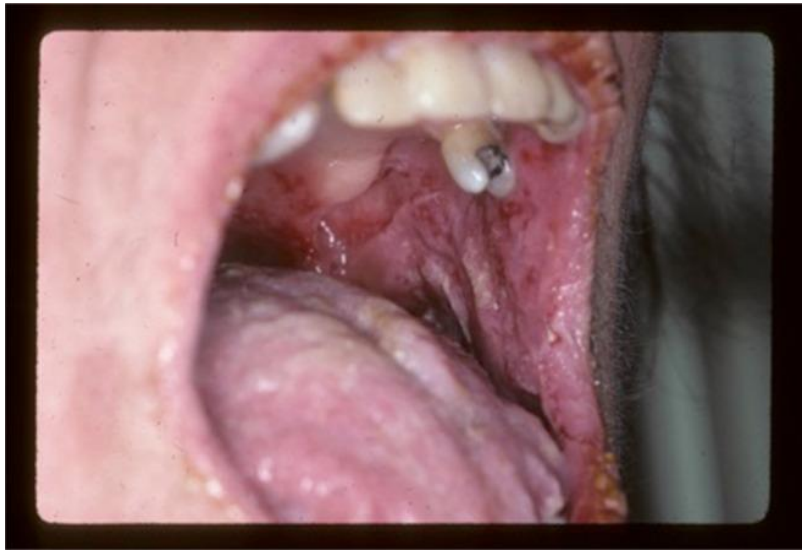




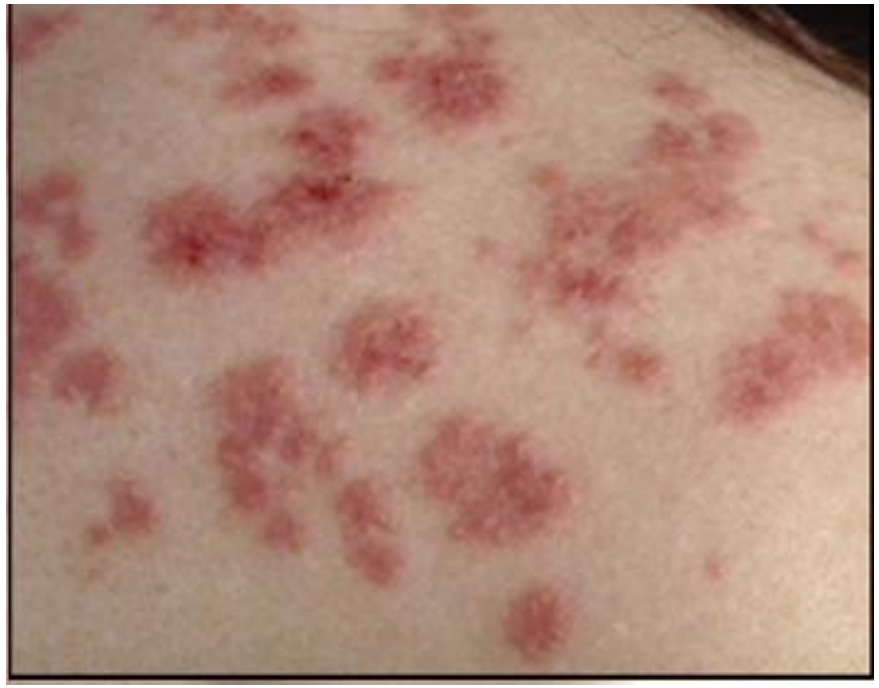
Dermatomyositis (DM)	Heliotrope rash (violaceous, edematous rash on upper eyelids); Gottron papules (scaly papules on bony surfaces); erythematous rash on face, neck, chest, back, or shoulders (the last of which is known as *shawl sign*); rash may be photosensitive; proximal muscle weakness; swallowing difficulty; respiratory difficulty; muscle pain	Laboratory findings: elevated serum CK, AST, ALT, LDH, and aldolase; EMG: increased spontaneous activity with fibrillations, complex repetitive discharges, and positive sharp waves; Muscle biopsy: perivascular or interfascicular septal inflammation and perifascicular atrophy	Ovarian, breast, prostate, lung, colorectal, non-Hodgkin lymphoma, naso-pharyngeal
Hypertrophic osteo-arthropathy	Subperiosteal new bone formation on phalangeal shafts ("clubbing"), synovial effusions (mainly large joints), pain, swelling along affected bones and joints	Plain radiography: periosteal reaction along long bones Nuclear bone scan: intense and symmetric uptake in long bones	Intrathoracic tumors, metastases to lung, metastases to bone, nasopharyngeal carcinoma, rhabdomyosarcoma
Polymyalgia rheumatica (PMR)	Limb girdle pain and stiffness	Laboratory findings: elevated serum ESR (often not as high as in nonparaneoplastic PMR) and CRP	Leukemia/lymphoma; myelodysplastic syndromes; colon; lung; renal; prostate; breast



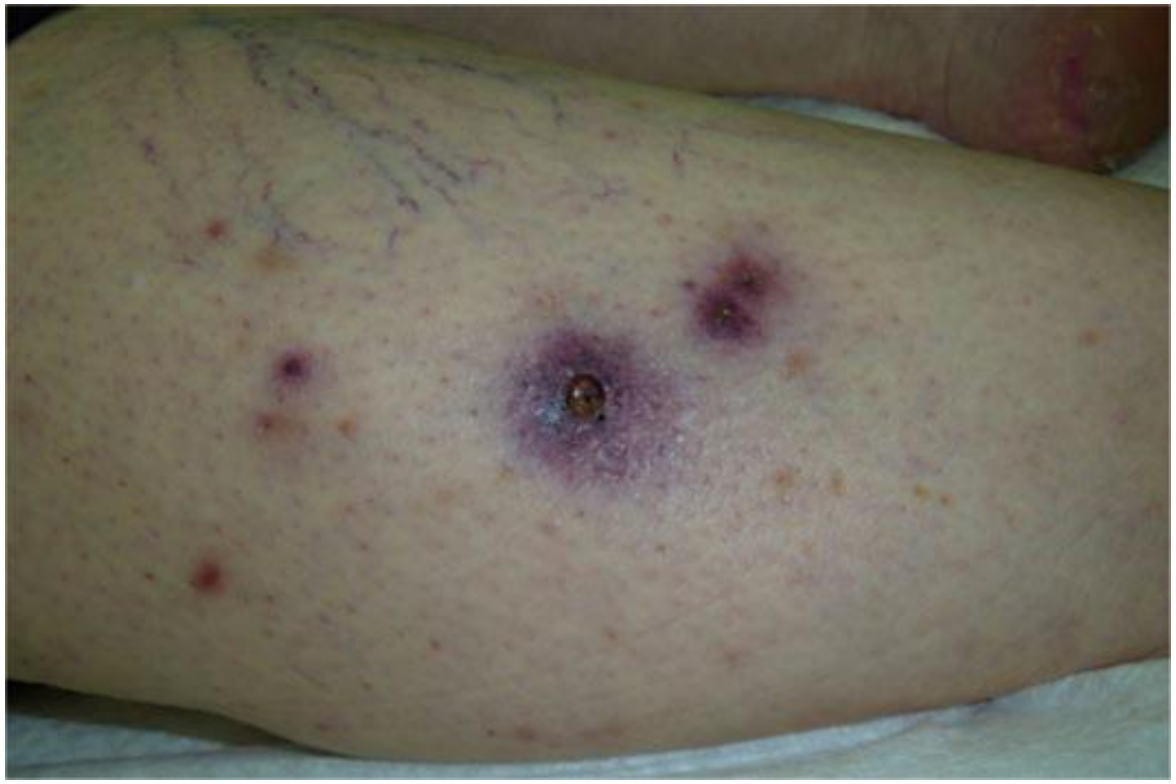
Acanthosis nigricans	Velvety, hyperpigmented skin (usually on flexural regions); papillomatous changes involving mucous membranes and muco-cutaneous junctions; rugose changes on palms and dorsal surface of large joints (eg, tripe palms)	Skin biopsy: histology shows hyperkeratosis and papillomatosis	Adenocarcinoma of abdominal organs, especially gastric adenocarcinoma (~90% of malignancies in patients with acanthosis nigricans are abdominal); gynecologic



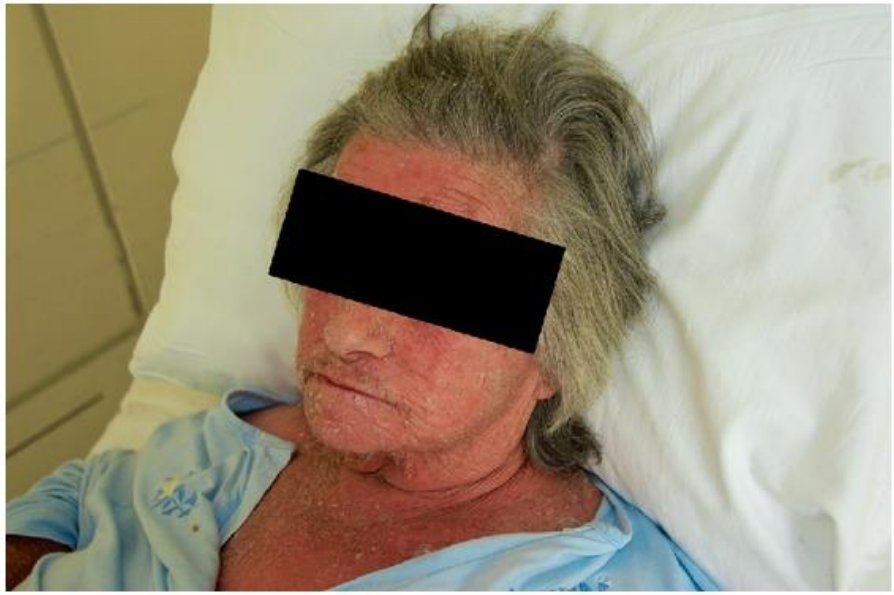
Paraneoplastic pemphigus (PNP)	Severe cutaneous blisters and and erosions (predominantly on trunk, soles, palms); severe mucosal erosions, including stomatitis	Serum antibodies to epithelia (against plakin proteins and desmogleins) Skin biopsy: histology shows keratinocyte necrosis, epidermal acantholysis, and IgG and complement deposition in epidermal and basement membrane zones	Non-Hodgkin lymphoma, chronic lymphocytic leukemia, thymoma, Castleman disease, follicular dendritic cell sarcoma



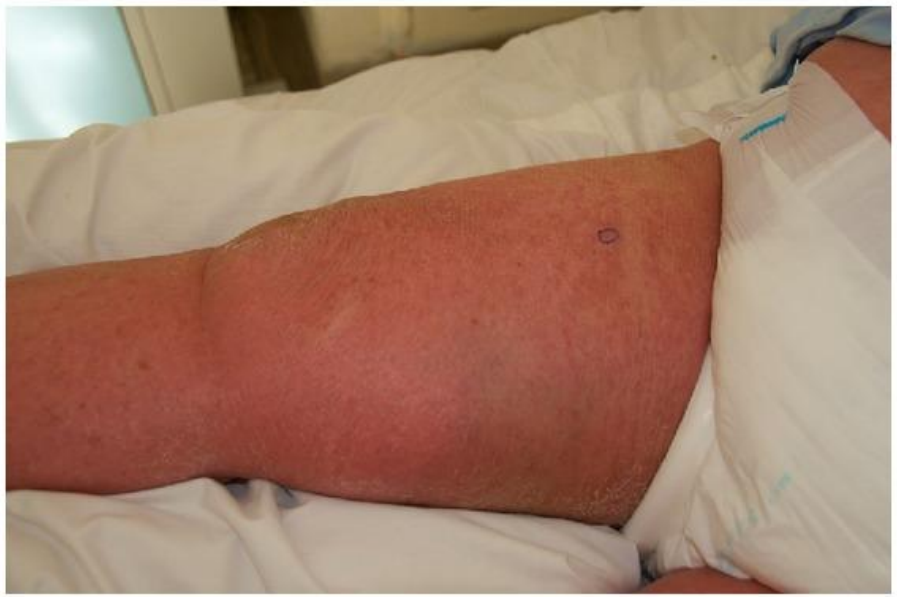
Sweet syndrome (acute febrile neutrophilic dermatosis)	Acute onset of tender, erythematous nodules, papules, plaques, or pustules on extremities, face, or upper trunk; neutrophilia; fever; malaise	Skin biopsy: histology shows a polymorphonuclear cell dermal infiltrate	Leukemia (especially AML), non-Hodgkin lymphoma, myelodysplastic syndromes, genitourinary, breast, GI, multiple myeloma, gynecologic, testicular, melanoma



Leukocytoclastic vasculitis	Ulceration, cyanosis, and pain over affected regions (especially digits); palpable purpura, often over lower extremities; renal impairment; peripheral neuropathy	Skin biopsy: histology shows fibrinoid necrosis, endothelial *swelling*, leukocytoclasis, and RBC extravasation	Leukemia/lymphoma, myelodysplastic syndromes, colon, lung, urologic, multiple myeloma, rhabdomyosarcoma



(a)



(b)

Erythroderma	Erythematous, exfoliating, diffuse rash (often pruritic)	Skin biopsy: histology shows dense perivascular lymphocytic infiltrate	Chronic lymphocytic leukemia, cutaneous T-cell lymphoma (including mycosis fungoides), GI (colorectal, gastric, esophageal, gallbladder), adult T-cell leukemia/ lymphoma, myeloproliferative disorders

Οφθαλμός (1)

Paraneoplastic syndrome	Underlying neoplasm	Circulating antibodies in peripheral blood	Clinical findings	Histopathological findings	Genetic findings	Source
CAR	small-cell carcinoma of the lung, other neoplasm of the lung, breast cancer, cancers of the cervix, ovary, uterus and thymus, osteosarcoma, Warthin tumor of parotid gland, prostate, pancreatic neuroendocrine, small bowel, bladder and laryngeal neoplasms, lymphomas (systemic follicular cell lymphoma) and colon adenomas	Recoverin (23-kDa), retinal enolase (46-kDa), TULP1, hsc-70 and 60, AIPL1, IRBP, PNR, GAPDH (36-kDa), aldolase C (40-kDa), transducin-α possibly: GCAPs, HSP27 and Rab6A, CA II (30-kDa), CRMP5 and anti-Hu, antiretinal autoantibodies against 48-kDa (arrestin) and 64-kDa and 94-kDa	cone dysfunction: photosensitivity, prolonged glare, decreased BCVA, color discrimination and central scotomas; rode dysfunction: night blindness, prolonged adaptation to darkness and peripheral or ring scotomas arteriolar narrowing, retinal pigment epithelial thinning and motting, vitritis, cells in anterior chamber, sheathing of retinal arterioles, periphlebitis and pallor of the optic disc	relatively small cells with little cytoplasm intensively positive for recoverin as well as positive for *NSE*, *Ki-67* and *tp53*	no additional data available apart from data that confirms the circulating antigens involvement	Weixler, Oertli and Nebiker 2016; Dalin et al. 2016; S. Yang et al. 2016; Adamus, Yang and Weleber 2016; Bhavsar et al. 2015; Adamus 2015; M. Morita et al. 2014; Turaka et al. 2014; Machida et al. 2014; Adamus, Choi, et al. 2013; M. Saito et al. 2014; Adamus, Bonnah, et al. 2013; Makiyama et al. 2013; W. Saito et al. 2013
CACD	small-cell endometrial cancer, primary cervical intraepithelial neoplasia, occult small cell lung carcinoma and laryngeal carcinoma	recoverin and protein whose molecular weight is 50 and 40 kDa	mild to moderate best-corrected visual acuity loss, sudden photosensitivity, total or subtotal loss of color perception, visual acuity improvement while wearing sunglasses	no data	no data	Finger, Thirkill and Borruat 2012; Javaid et al. 2015; Parc et al. 2006; Hargitai et al. 2004
MAR and MAR-like retinopathies	cutaneous melanoma	TRPM1, α-enolase, recoverin or hsc-70, CA II, IRBP, Bestrophin, myelin basic protein, mitofilin, titin, and rod outer segment proteins	sudden shimmering, flickering, difficulty with night vision and photopsias (pulsating continuous or intermittent) with occasional hyperphotosensitivity and floaters	local retinal thinning with the damaged inner nuclear layer and outer plexiform layer positive melanoma-associated autoantibodies directly against transient receptor potential M1 channels that target the ON-bipolar cell structures in the inner nuclear and outer plexiform layers in PVtR	no additional data available apart from data that confirms the circulating antigens involvement	Lincoff et al. 2016; Wang et al. 2012; Dalal et al. 2013; Xiong et al. 2013; Y. Morita et al. 2014; Dhingra et al. 2011; Aronow et al. 2012

Οφθαλμός (2)

Paraneoplastic syndrome	Underlying neoplasm	Circulating antibodies in peripheral blood	Clinical findings	Histopathological findings	Genetic findings	Source
BDUMP	ovarian, cervix, uterus, colon and rectum cancer, gallbladder cancer, neoplasm of the retroperitoneal space, and a variety of lung cancers	CMEP factor, AAbs against 35-kDa, 46-kDa, 30-kDa, 50-kDa, and 70-kDa proteins	classical findings: slow, painless, bilateral (usually asymmetric), progressive loss of vision for several months, subretinal infiltration and exudative retinal detachment that result as outer retinal damage development of cataract, iridocyclitis or glaucoma additional clinical findings: iris nodules, pigmented keratic precipitates, anterior chamber and vitreous cells, peripheral retinal arterial areas of non-perfusion, loss of RPE in a pattern described as nummular or dermal, conjunctival melanocytic proliferation	infiltration consisted of more benign-appearing melanocytes – stained positively with melan-A	deletions in chromosome 19, gain in chromosomes 5, 6, 8q and X lack of mutations in *GNAQ*, *GNA11* and $BRAF^{V600F}$	Mittal et al. 2015; Mudhar et al. 2012; Rahimy, Coffee and McCannel 2015; Lin and Mruthyunjaya 2012; Navajas et al. 2011; Yonekawa, Shildkrot and Eliott 2013; Pulido et al. 2013; Jansen et al. 2015; Adamus et al. 2013; Miles et al. 2012
PON	adenocarcinoma and small cell carcinoma of the lung, prostate carcinoma, stomach carcinoid tumor, colon adenocarcinoma, cutaneous melanoma, occult pancreatic non-secretory neuroendocrine tumor, thymoma	CRMP5, aquaporin 4, MBP, ANNA-1, recoverin, enolase	neuroretinitis and positive autoantigens against neuronal part of retina and the optic nerve	no histological data available in recent papers due to tissue sampling consequences concerning visual function	no additional data available apart from data that confirms the circulating antigens involvement	Verschuur, Kooi and Troost 2015; M. Saito et al. 2014; Adamus et al. 2011; Finger, Thirkill and Borruat 2012; Carboni et al. 2012; Al-Harbi et al. 2014; Chao et al. 2013; Slamovits et al. 2013; Schoenberger, Kim and Lavin 2012; H. K. Yang et al. 2014; Iyer et al. 2014

CAR – cancer-associated retinopathy; CACD – cancer-associated cone dysfunction; MAR – melanoma-associated retinopathy; BDUMP – bilateral diffuse uveal melanocytic proliferation; BCVA – best-corrected visual acuity; RPE – retinal pigment epithelium; PON – paraneoplastic optic neuritis; PVtR – paraneoplastic vitelliform retinopathy; *TULP1* – Tubby-like protein 1; hsc-70 – heat shock cognate protein 70; *TRPM1* – transient receptor potential cation channel; subfamily M member 1 (that is labeled on ON-bipolar cells); CA II – carbonic anhydrase II; IRBP – interphotoreceptor retinoid binding protein; CMEP factor – cultured melanocyte elongation and proliferation factor; CRMP5 – collapsin response mediator protein 5; MBP – myelin binding protein; ANNA-1 – type 1 antineuronal nuclear antibody; *GCAPs* – guanylyl cyclase-activating proteins; HSP27 – heat shock protein 27; *Rab6A* – Rab6A GTPase; PNR – photoreceptor cell-specific nuclear receptor; *GAPDH* – glyceraldehyde 3-phosphate dehydrogenase; *AIPL1* – aryl hydrocarbon receptor interacting protein-like 1.

ΣΥΜΠΕΡΑΣΜΑΤΑ

- Συνεργασία
- Συνεργασία
- Συνεργασία

A 63-year-old male is seen in the clinic and found to have a metastatic cancer. Which of the following features is not associated with a malignancy?

1. Acanthosis nigricans
2. Migratory thrombophlebitis
3. Eaton Lambert syndrome
4. Erythema multiforme

A patient with lung cancer has excessive production of calcium. Which of the following statements is incorrect?

1. Hypercalcemia will produce mental changes including somnolence
2. Patients may have anorexia and vomiting
3. The tumor is not resectable
4. Excision of the tumor will reverse hypercalcemia

Which histologic type of lung cancer is most frequently associated with hypercalcemia?

1. Small cell
2. Squamous cell
3. Adenocarcinoma
4. Carcinoid

Which of the following hormones is not produced by paraneoplastic syndromes?

1. Antidiuretic hormone
2. Adrenocorticotropic hormone
3. Serotonin
4. Enkephalin

Which of the following paraneoplastic syndromes is not seen with lung cancers?

1. Hypercalcemia
2. ADH secretion
3. Hyperglycemia
4. Eaton Lambert syndrome