Les syndromes paranéoplasiques

Enseignement interuniversitaire du tronc commun en médecine interne

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Définition

- Entité complexe, relativement rare (8 % des cancers: poumon, sein, digestif…)
- Ne peuvent pas par définition être produits par un effet direct de la tumeur ou de ses métastases
- Peuvent être la première manifestation du cancer
- Evolution pas forcément parallèle au cancer
- Mécanismes: sécrétion peptide, hormonal, immunitaire, cytokines

Cas clinique: F 58 ans

- février: attaque de panique
- 10 mars: impression d'avoir des brûlures dans la poitrine, puis des hallucinations visuelles
- 13 mars: crise d'épilepsie généralisée

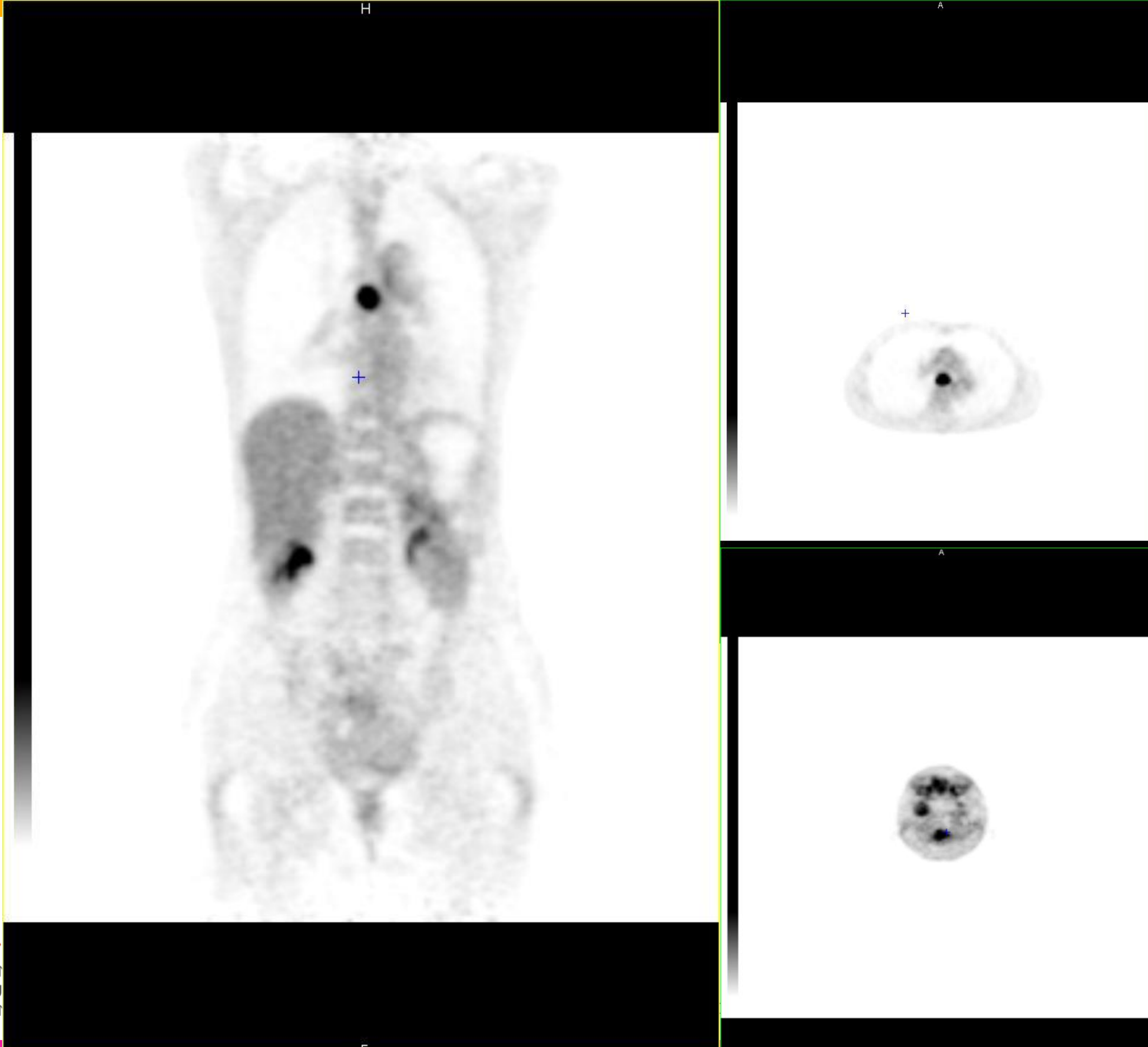
  RMN cérébrale: normale

  R/ lévétiracétam
- 24 mars: désorientation, amnésie, perte de mémoire à court terme

Examen physique

TA: 13/8. RC régulier 100/minute. T°36,5
Il n'y a pas d'adénopathie cervicale palpée.
Auscultation cardio-pulmonaire normale.
Abdomen souple, dépressible, indolore, péristaltique.
Pas d'OMI et pas de signe de TVP
Légère désorientation dans le temps et l'espace.
Elocution normale, rapide mais cherche de temps en temps ses mots.
Les pupilles sont isocores et réflectiques.
La force est normale.
La marche est normale .
Les réflexes sont normaux.
Il n'y a pas d'hippocratisme digital.

- **Biologie**: normale
- **EEG:** ralentissement temporal gauche.
- **RMN cérébrale**: au niveau temporal hypersignal des 2 hippocampes avec prise de contraste au niveau de l'hippocampe gauche, hypersignal cortico-sous-cortical des lobes frontaux et pariétaux
- **Ponction lombaire**: protéines à 607 mg/l, 2000 GR /mm³ , GB 7/mm³, cytologie négative, PCR HSV, VZV et entérovirus négatives, pas de bandes oligo-clonales.
- **Scanner thoracique**: ADP 15 mm en sous-carinaire, ADP juxta-centimétriques en latéro-trachéal droit, une petite opacité nodulaire du lobe moyen de 9 mm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Quel est votre diagnostic?

Encéphalite limbique para-néoplasique sur carcinome bronchique à petites cellules localement avancé.

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Sur base de quels critères?

Encéphalite limbique

<u>Critères diagnostiques</u>:

1. Début subaigu (< 3 mois): pertes de mémoire, épilepsie, symptômes psychiatriques
2. Anomalies cérébrales bilatérales temporales en T2 (RMN)
3. Pléocytose (GB>5/mm^3) au LCR ou activité épileptique ou ralentie au niveau temporal à l'EEG
4. Exclusion d'autres causes plus probables

Encéphalite limbique

- Les symptômes neurologiques précèdent le diagnostic de cancer dans 65% des cas
- 50 à 75% des cas sont associés à un cancer bronchique
- Anti-Hu + dans 50% des CBPC

Table 2
Onconeural antibodies (adapted from [9] and [206]).

Antibody	Antigen	Paraneoplastic neurological syndrome
Well characterised onconeuronal antibodies		
Anti-Hu (ANNA1)	HuB (Hel-N1)/ELAVL2, HuC/ELAVL3, HuD/ELAVL4	Encephalomyelitis; sensory neuronopathy; chronic gastrointestinal pseudo-obstruction; paraneoplastic cerebellar degeneration; limbic encephalitis
Anti-Yo (PCA1)		Paraneoplastic cerebellar degeneration
Anti-CRMP5	Collapsin response mediator protein (CRMP5/POP66)	Encephalomyelitis; chorea; sensory neuronopathy; sensorimotor neuropathy; chronic gastrointestinal pseudo-obstruction; paraneoplastic cerebellar degeneration; limbic encephalitis; LEMs, optical neuropathy
Anti-CV2	CRMP3	
Anti-Ri (ANNA2)/anti-Nova	Neuro-oncological ventral antigen (Nova)	brainstem encephalitis (including OMS), cerebellar syndrome, encephalopathy, peripheral neuropathy
Anti-Ma2	Paraneoplastic Ma proteins (PNMA1)	Limbic/diencephalic encephalitis; brainstem encephalitis/paraneoplastic cerebellar degeneration
Anti-Ta	PNMA2	Paraneoplastic encephalomyelitis/sensory neuronopathy
Anti-amphiphysin	Amphiphysin	Stiffman syndrome; various syndromes
Surface-binding autoantibodies		
Anti-VGCC	P/Q type voltage-gated calcium channel (VGCC), MysB	Lambert-Eaton syndrome; paraneoplastic cerebellar degeneration
Anti-LGI1 (ex-anti-VGKC)	Protein complex anchoring VGKC (leucine-rich glioma-inactivated 1)	Limbic encephalitis; multifocal neurological involvement; sleep disorders
Anti- CASPR2 (other ex-anti-VGKC)	Protein complex anchoring VGKC (contactin-associated protein-like 2)	Morfan syndrome; neuromyotonia
Anti-AMPAR; Anti-GluR1/2	α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor (AMPAR)	Lambert-Eaton syndrome, paraneoplastic cerebellar degeneration; limbic encephalitis
Anti-$GABA_B$ R	$GABA_B$ receptor	Lambert-Eaton syndrome; limbic encephalitis
Anti-AChR (α3)	Nicotinic acetylcholine receptors (AChRs)	Autonomic neuropathy; peripheral neuropathies; encephalopathy
Anti-NMDAR	*N*-methyl-D-aspartate receptor	Encephalitis
NMO	Neuromyelitis optica IgG	Neuromyelitis optica
Partially characterised onconeuronal antibodies		
Anti-Tr (PCA-Tr)		Paraneoplastic cerebellar degeneration –
Anti-neuronal nuclear autoantibody type 3 (ANNA-3)	170-kDa brain protein	Sensory/sensorimotor neuropathies, cerebellar ataxia, myelopathy, brain stem and limbic encephalopathy
PCA2Anti-Purkinje cell cytoplasmic antibody (PCA)-2	280-kDa cerebellar protein	Various
Anti-BRSK2	BR serine/threonine kinase (BRSK)2	Limbic encephalitis
Anti-Zic	ZIC2 ZIC4 (derived from zinc fingers of cerebellum)	Paraneoplastic cerebellar degeneration
Anti-GAD65 (GAD65A)	Glutamic acid decarboxylase (GAD) 2	Encephalomyelitis and rigidity
Antiretinal, Anti-Rc	Recoverin	Cancer-associated retinopathy
Anti-SOX	Sry-like high mobility group box (SOX)1,2	Lambert-Eaton syndrome, paraneoplastic cerebellar degeneration

Anna-1: Type 1 antineuronal nuclear antibody; PCA-1: Purkinje Cell Cytoplasmic Antibody, Type 1; CRMP-5: collapsin response-mediator protein 5.

Cas clinique

- Anti-YO , anti-Hu négatifs
- anti-GABA, AMPAR, NMDAR 14:3:3 négative

Amphiphysin: Negative, Cv2: Negative,
PNMA2/Ta (Ma2/Ta): Negative, Ri: Negative
Recoverin: Negative, SOX1: Negative,
Titin: Negative, Zic4: Negative
GAD65: Negative, Tr (DNER): Negative

Autoimmune paraneoplastic syndromes associated to lung cancer: A systematic review of the literature
Part 3: Neurological paraneoplastic syndromes, involving the central nervous system

Georgiana Bentea[a], Claudine Sculier[a], Bogdan Grigoriu[a], Anne-Pascale Meert[a,c], Valérie Durieux[b,c], Thierry Berghmans[a,c], Jean-Paul Sculier[a,c,*]

Table 1
Paraneoplastic neurological syndromes documented with lung cancer (adapted from [4]).

Central nervous system

- Limbic encephalitis* (LE)
- Encephalomyelitis* (PEM)
- Brainstem encephalitis
- Stiff-person syndrome (SMS)
- Opsoclonus-myoclonus* (OMS)
- Cerebellar degeneration* (PCD)
- Extrapyramidal disease/chorea
- Necrotizing myelopathy, myelitis
- Paraneoplastic visual syndromes : cancer-associated retinopathy (CAR), paraneoplastic optic neuropathy (PON)
- Motor neuron syndromes : subacute motor neuronopathy; other motor neuron syndromes

- Peripheral nervous system
- Acute and chronic polyradiculitis
- Acute sensorimotor neuropathy
- Subacute sensory neuronopathy*
- Chronic sensorimotor neuropathy
- Brachial neuritis
- Acute pandysautonomia
- Chronic gastrointestinal pseudo-obstruction*
- Paraneoplastic peripheral nerve vasculitis

- Neuromuscular junction and muscle
- Myasthenia gravis
- Lambert-Eaton syndrome* (LEMS)
- Polymyositis/dermatomyositis*
- Acute necrotizing myopathy
- Cachectic myopathy
- Neuromyotonia

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Lung Cancer 106 (2017) 83–92

Recommended diagnostic criteria for paraneoplastic neurological syndromes

F Graus, J Y Delattre, J C Antoine, J Dalmau, B Giometto, W Grisold, J Honnorat, P Sillevis Smitt, Ch Vedeler, J J G M Verschuuren, A Vincent, R Voltz, for the Paraneoplastic Neurological Syndrome Euronetwork

See Editorial Commentary, p 1090

J Neurol Neurosurg Psychiatry 2004;**75**:1135–1140. doi: 10.1136/jnnp.2003.034447

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Syndrome neurologique paranéoplasique « défini »

- un « syndrome classique » et un cancer se développant dans les 5 ans suivant le début du syndrome neurologique. Dans ce cas, la présence d'anticorps onconeuronaux n'est pas requise
- un « syndrome non classique » qui s'améliore après le traitement du cancer sans immunothérapie, pourvu que le syndrome n'ait pas eu de rémission spontanée. Une stabilisation du syndrome peut représenter une réponse au traitement de la tumeur avec une amélioration limitée par des dégâts neurologiques irréversibles
- un « syndrome non classique » avec des anticorps onconeuronaux et un cancer se développant dans les cinq ans suivant le début du syndrome neurologique
- un syndrome neurologique (« classique » ou pas) avec des anticorps onconeuronaux bien caractérisés (anti-Hu, Yo, CV2, Ri, Ma2, amphiphysine) et pas de cancer.

Syndrome neurologique paranéoplasique « probable »

- un syndrome classique, sans anticorps onconeuronaux et sans cancer ; mais à haut risque d'avoir une tumeur sous-jacente. Le diagnostic de cancer pendant l'évolution de la pathologie est la seule chose qui manque pour qualifier le syndrome neurologique paranéoplasique de « défini »
- un syndrome neurologique (« classique » ou pas) avec des anticorps onconeuronaux partiellement caractéristiques et sans cancer
- un « syndrome non classique », sans anticorps onconeuronaux et présence de cancer dans les deux ans suivant le diagnostic. Cette définition inclut des syndromes neurologiques pour lesquels on ne peut exclure l'association occasionnelle avec un événement aussi fréquent que le cancer. Le délai est limité à deux ans pour limiter cette possibilité.

Recommended diagnostic criteria for paraneoplastic neurological syndromes

F Graus, J Y Delattre, J C Antoine, J Dalmau, B Giometto, W Grisold, J Honnorat, P Sillevis Smitt, Ch Vedeler, J J G M Verschuuren, A Vincent, R Voltz, for the Paraneoplastic Neurological Syndrome Euronetwork

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Table 1 Classical and non-classical paraneoplastic neurological syndromes

Syndromes of the central nervous system
Encephalomyelitis
Limbic encephalitis
Brainstem encephalitis
Subacute cerebellar degeneration
Opsoclonus-myoclonus*
Optic neuritis†
Cancer associated retinopathy†
Melanoma associated retinopathy†
Stiff person syndrome
Necrotising myelopathy‡
Motor neuron diseases‡
Syndromes of the peripheral nervous system
Subacute sensory neuronopathy
Acute sensorimotor neuropathy
Guillain-Barré syndrome‡
Brachial neuritis‡
Subacute/chronic sensorimotor neuropathies*
Neuropathy and paraproteinaemia†
Neuropathy with vasculitis‡
Autonomic neuropathies
Chronic gastrointestinal pseudo-obstruction
Acute pandysautonomia‡
Syndromes of the neuromuscular junction and muscle
Myasthenia gravis†
Lambert-Eaton myasthenic syndrome‡
Acquired neuromyotonia‡
Dermatomyositis‡
Acute necrotising myopathy‡

Classical syndromes are underlined.
*Associated with onconeural antibodies only with particular tumour types.
†Syndromes not included in the present recommendations.
‡Neurological syndromes not associated with known onconeural antibodies.

Traitement?

Traitement

Traitement du cancer!

REVIEW

Paraneoplastic Syndromes: An Approach to Diagnosis and Treatment

LORRAINE C. PELOSOF, MD, PHD, AND DAVID E. GERBER, MD

Recent medical advances have improved the understanding, diagnosis, and treatment of paraneoplastic syndromes. These disorders arise from tumor secretion of hormones, peptides, or cytokines or from immune cross-reactivity between malignant and normal tissues. Paraneoplastic syndromes may affect diverse organ systems, most notably the endocrine, neurologic, dermatologic, rheumatologic, and hematologic systems. The most commonly associated malignancies include small cell lung cancer, breast cancer, gynecologic tumors, and hematologic malignancies. In some instances, the timely diagnosis of these conditions may lead to detection of an otherwise clinically occult tumor at an early and highly treatable stage. Because paraneoplastic syndromes often cause considerable morbidity, effective treatment can improve patient quality of life, enhance the delivery of cancer therapy, and prolong survival. Treatments include addressing the underlying malignancy, immunosuppression (for neurologic, dermatologic, and rheumatologic paraneoplastic syndromes), and correction of electrolyte and hormonal derangements (for endocrine paraneoplastic syndromes). This review focuses on the diagnosis and treatment of paraneoplastic syndromes, with emphasis on those most frequently encountered clinically. Initial literature searches for this review were conducted using PubMed and the keyword *paraneoplastic* in conjunction with keywords such as *malignancy*, *SIADH*, and *limbic encephalitis*, depending on the particular topic. Date limitations typically were not used, but preference was given to recent articles when possible.

Mayo Clin Proc. 2010;85(9):838-854

In some instances, paraneoplastic syndromes are manifest before a cancer diagnosis. Thus, their timely recognition may lead to detection of an otherwise clinically occult tumor at an early and highly treatable stage. Such a scenario occurs most commonly with neurologic paraneoplastic disorders. Although considerable clinical overlap with nonparaneoplastic disorders has long confounded the diagnosis of these conditions, numerous serologic and radiographic studies are currently available to aid in this process.

It is estimated that paraneoplastic syndromes affect up to 8% of patients with cancer.[3] As patients with cancer live longer, and as diagnostic methods improve, this prevalence will likely increase. Yet, given the rarity of individual paraneoplastic syndromes, there are few prospective clinical trials to guide management. However, paraneoplastic syndromes frequently represent subtypes of conditions that also occur outside of a cancer association. This review incorporates clinical experience from case series of specific paraneoplastic disorders, as well as larger studies of clinically similar, nonparaneoplastic conditions, to provide an overview of the diagnosis and treatment of the most commonly encountered paraneoplastic syndromes.

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TABLE 2. **Paraneoplastic Neurologic Syndromes**[a]

Syndrome	Clinical presentation	Associated antibodies[b]	Diagnostic studies	Associated cancers	Treatment options[b]
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	IVIG, 400-1000 mg/d to total 2-3 g Methylprednisolone, up to 1 g/d IV Prednisone, 1 mg/kg per day orally Plasma exchange Cyclophosphamide, ~2 mg/kg/d orally Rituximab, 375 mg/m^2 IV per dose

Syndromes paranéoplasiques

- Syndromes neurologiques
- Syndromes cutanés
- Syndromes endocriniens
- Syndromes métaboliques
- Syndromes rhumatologiques
- Syndromes cardiovasculaires
- Syndromes hématologiques
- Syndromes digestifs
- Syndromes néphrologiques
- Manifestations générales

Syndromes quasi toujours paranéoplasiques

Syndrome de Lambert-Eaton

Résultat d'un blocage immunologique des canaux calciques voltage-dépendants situés sur l'élément présynaptique de la jonction neuromusculaire

- Contexte
  - 50% des cas : associé à un CBPC
  - multiples autres tumeurs solides et hématologiques
- Tableau clinique: souvent insidieux
  - faiblesse des membres inférieurs (avec difficulté à la marche) ou des membres supérieurs ou fatigabilité d'amélioration à la répétition de l'effort
  - symptômes oculobulbaires: ptosis, diplopie, dysarthrie, dysphagie
  - paresthésies des membres ou péribuccales
  - atteinte du système nerveux autonome : sécheresse buccale, troubles de l'accommodation, constipation, troubles de l'érection
  - perte de poids (cancer)
- Diagnostic
  - EMG: amplitude réduite des réponses motrices s'améliorant à l'effort (facilitation) (avec vitesse de conduction normale)
  - AC circulants anti-canaux calciques voltage-dépendants

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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	3,4-DAP, maximum of 80 mg/d orally Guanidine, ~575 mg/d orally (with pyridostigmine) Pyridostigmine, ~240-360 mg/d orally (with guanidine) Prednisolone, 60-100 mg orally every other day Azathioprine, up to 2.5 mg/kg/d orally IVIG, 400-1000 mg/d to total 2-3 g Plasma exchange

Syndrome de Pierre Marie Bamberger

CBNPC (80 %)

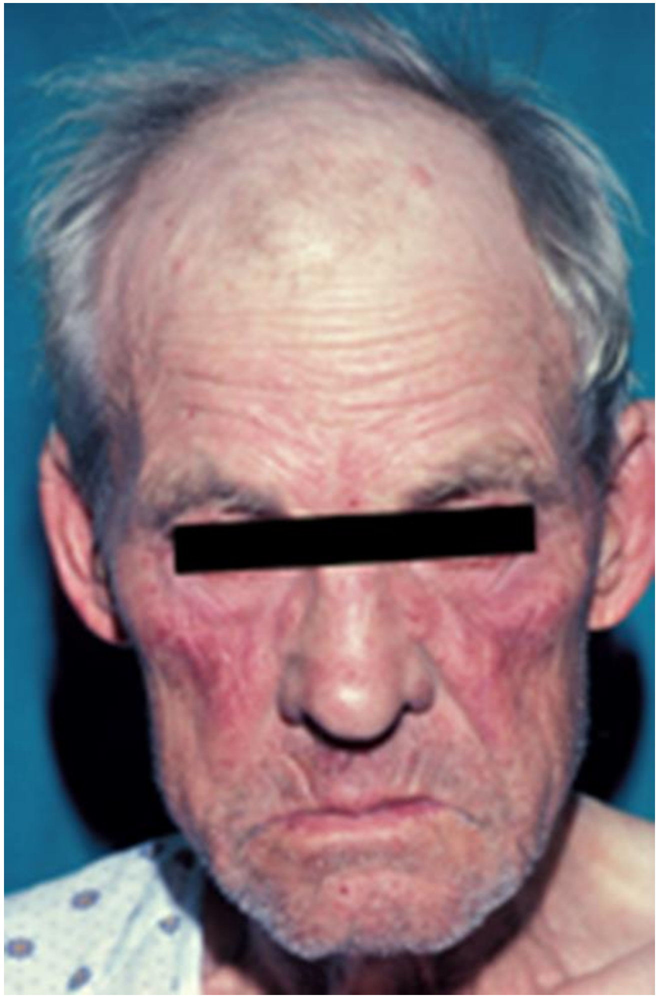
Hippocratisme digital, hypertrophie des extrémités, hyperplasie cutanée, arthropathies

Périostose radiologique: avant-bras, jambes

Hippocratisme digital isolé : ΔΔ BPCO, cardiopathies cyanogènes

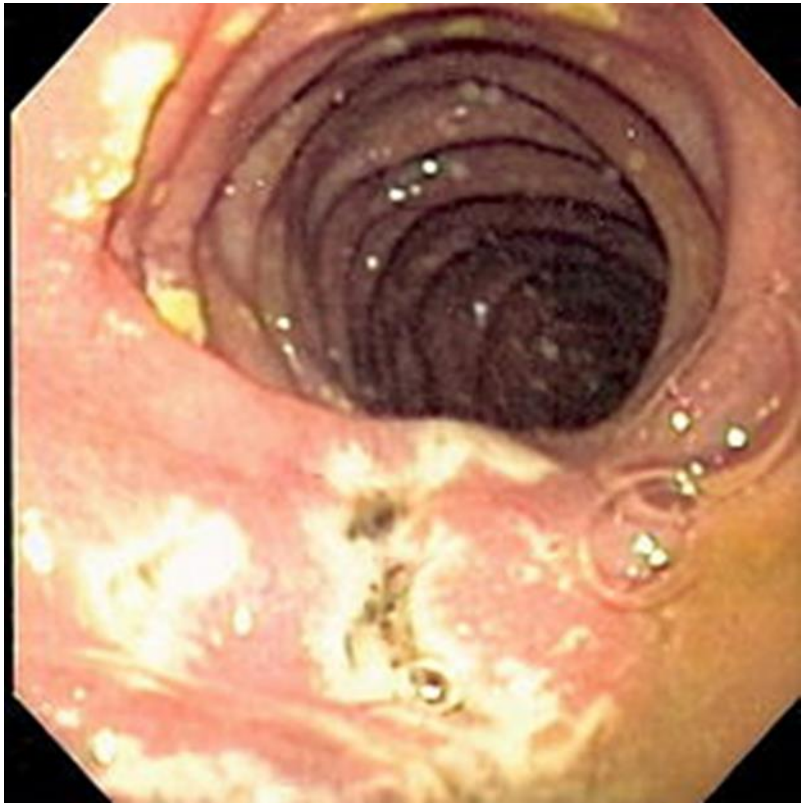
Syndrome carcinoïde

- Tumeur carcinoïde digestive avec métastases hépatiques (> 95 %), carcinoïdes bronchiques ou ovariens
- flush cutané, diarrhée, bronchospasme, érythème facial chronique avec télangiectasies, troubles psychiatriques
  - Spontané ou facteur déclenchant (émotion, alcool, effort physique)
- Tardivement : atteinte cardiaque (le plus souvent droite)
- Diagnostic: dosage 5HIAA urinaire



Syndrome de Zollinger-Ellison

- gastrinome pancréatique le plus souvent malin
- Ulcères multiples, de siège atypique (postbulbaire), d'évolution sévère et récidivante; souvent associés à une diarrhée
- hypersecrétion acide basale, hypergastrinémie avec augmentation paradoxale après injection de sécrétine
- Parfois associé à d'autres tumeurs endocrine (NEM I ou syndrome de Wermer)



Acrokératose de Bazex

Epithélioma épidermoïde VADS (90 %)

Érythème gyratum repens de Gammel

Exceptionnel
Néo poumon, digestif haut, sein
Bandes érythémateuses, circinées, migratrices, très prurigineuses (cou, tronc)
Parfois associée à hyperéosinophilie

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Érythème nécrolytique migrateur

- Glucagonome (70 %), malin dans 80 % des cas
- Fréquence élevée de métastases hépatiques
- Placards érythémateux eczémateux ou psoriasiforme à centre bulleux puis nécrotique (extrémités, visage)
- État général altéré
- Taux élevé de glucagon
- Histologie très suggestive

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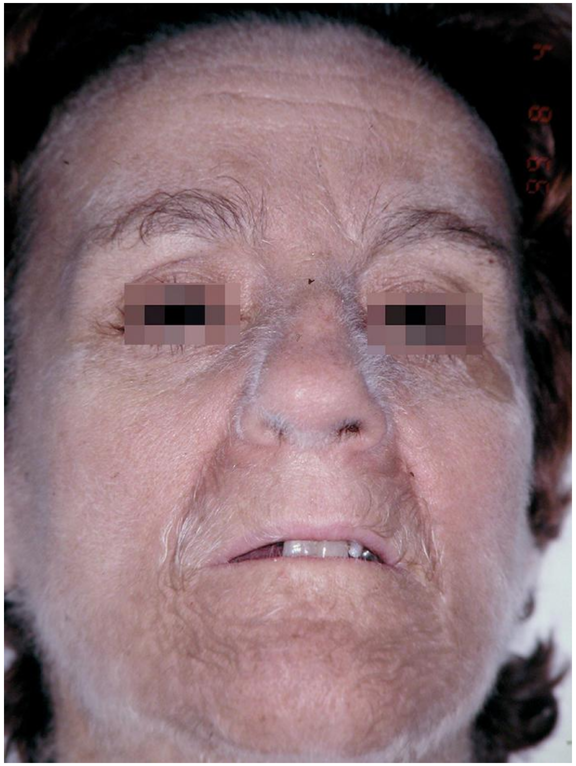
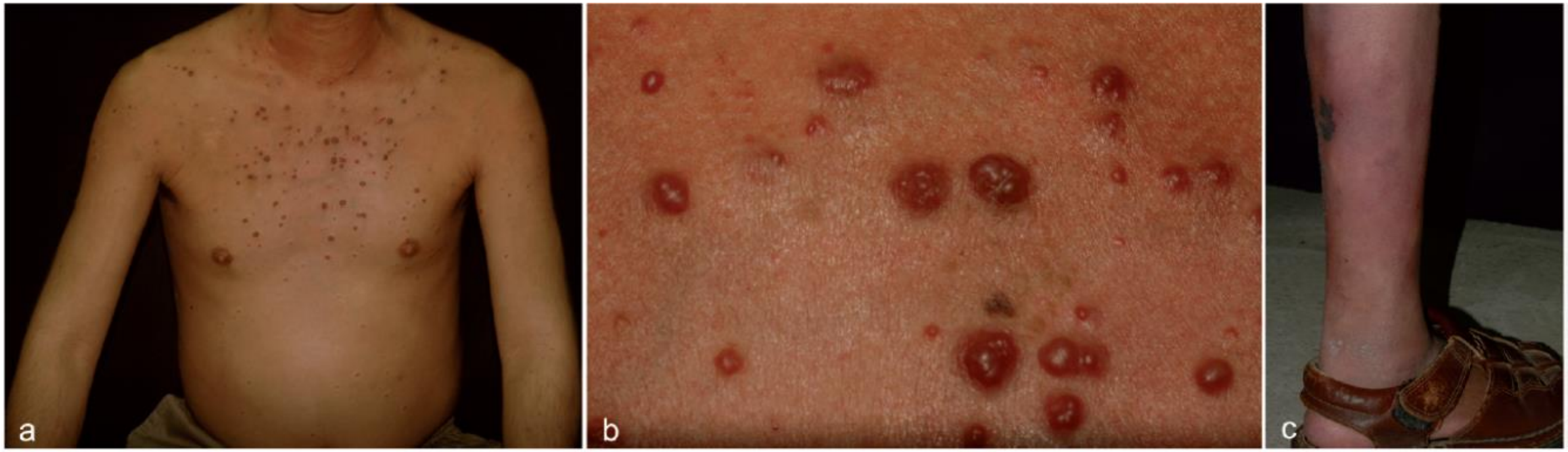
Hypertrichose lanugineuse acquise



- Cancers colique, poumon, sein, rein et lymphomes
- Exceptionnel
- Poils longs et fins, blonds ou blancs, d'apparition rapide au visage, nuque et tronc (sans modification de la pilosité normale)

Syndrome POEMS (ou de Crow-Fukase)



- Plasmocytome, myélome multiple
- Tableau :
  - polyneuropathie (sensitivomotrice chronique)
  - organomégalie (foie, rate, ganglions, parotides)
  - endocrinopathies (gynécomastie, impuissance, aménorrhée; rarement diabète sucré)
  - modifications cutanées (hyperpigmentation, hippocratisme, hypertrichose, leuconychie, angiomes cutanés, infiltration indurée)
  - gammopathie monoclonale

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Syndromes associés avec le cancer

- Endocrinien: SIADH, hypercalcémie, syndrome de Cushing, hypoglycémie, gynécomastie, galactorrhée
- Neurologique: myasthénie
- Dermatologique: syndrome de Sweet, ichtyose, signe de Leser-Trelat, pyoderma gangrenosum, syndrome des ongles jaunes, syndrome de Weber Christian, vascularite leucocytoclasique, amyloïdose, (dermato)polymyosite
- Cardiovasculaires: thromboses, endocardite marastique, syndrome de Raynaud
- Hématologique: anémie microangiopathique, anticoagulants circulants, CIVD, amyloïdose, anémie hémolytique auto-immune, érythroblastopénie, polyglobulie, hyperleucocytose, hyperéosinophilie, hyperplaquettose, thrombopénie
- Digestifs : malabsorption, anorexie – cachexie, entéropathies exsudatives, hyperamylasémie
- Néphrologiques : glomérulopathies, amyloïdose
- Généraux: fièvre, amyloïdose, prurit

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

Syndrome	Clinical presentation	Laboratory findings	Associated cancers
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
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

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
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

Myasthénie

- Thymome dans 15% des cas
- Faiblesse musculaire avec fatigabilité à l'effort (oculo-bulbaire, membres et diaphragme)
- Anti-AchR
- EMG: diminution de la réponse à la stimulation nerveuse répétitive

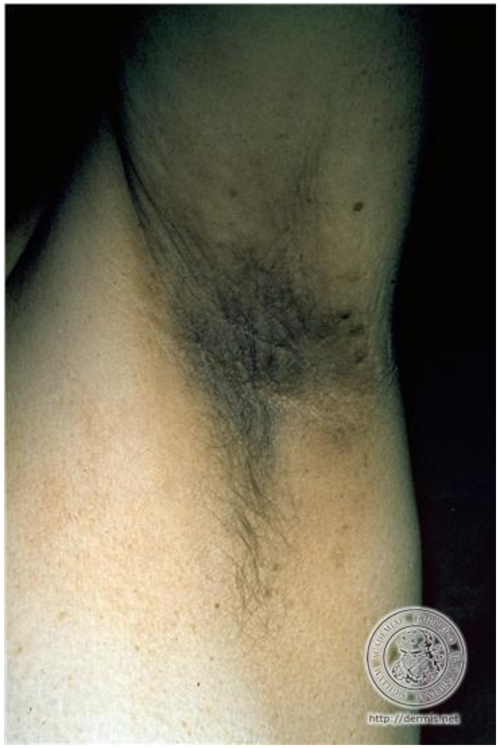
Myasthenia gravis (MG)	Fatigable weakness of voluntary muscles (ocular-bulbar and limbs), diaphragmatic weakness	anti-AchR	EMG: decremental response to repetitive nerve stimulation	Thymoma (in ~15% of MG patients)	Thymectomy Pyridostigmine, ~600 mg/d orally in divided doses Prednisone, ~1 mg/kg/d orally Azathioprine, up to 2.5 mg/kg/d orally (with corticosteroids) Cyclosporine A, ~3 mg/kg/d orally Tacrolimus, 3-4 mg/d orally Mycophenolate mofetil, 1-3 g/d orally Rituximab, 375 mg/m^2 IV per dose Cyclophosphamide, 50 mg/kg/d IV for 4 d Plasma exchange IVIG, 400-1000 mg/d to total 2-3 g

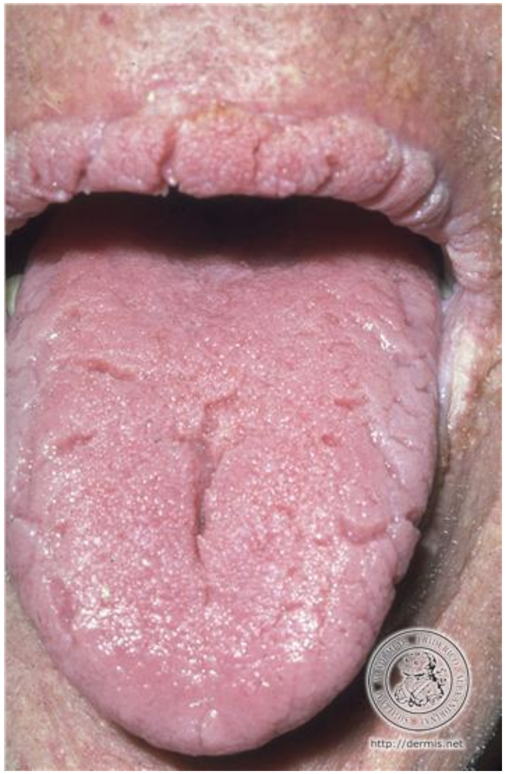
Syndrome de Sweet

- Peut être associé (20%des cas) à des hémopathies malignes (LAM) ou moins souvent à des tumeurs solides (GU, sein, GI)
- **Dermatose neutrophilique aigue fébrile** se caractérisant par
  - Fièvre
  - Neutrophilie
  - Plaques cutanées érythémateuses violacées douloureuses (MS, T&C) neutrophilique
  - Réponse rapide à la corticothérapie

Manifestations extracutanées possibles

Acanthosis Nigricans Maligna





- Adénocarcinomes (60%): gastriques
- Plaques hyperpigmentées hyperkératosiques
- Formes bénignes: familial, résistance à l'insuline, obésité, médicaments

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Signe de Leser-Trélat

- Adénocarcinomes digestifs, lymphomes non HK
- Kératoses séborrhéiques prurigineuses multiples de survenue brutale
- DD : kératose séborrhéique multiple banale du sujet âgé

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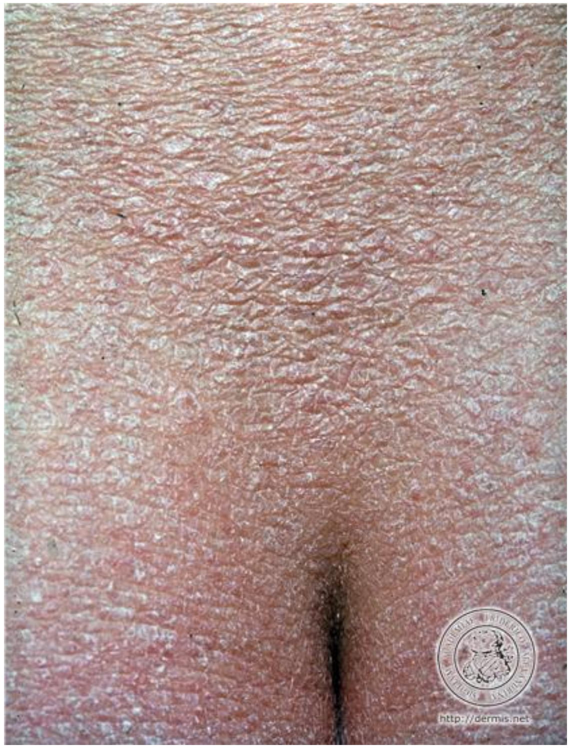
Acanthosis palmaire

- Cancer gastrique et bronchique
- Épaississement paumes avec aspect velouté, rugueux

Ichtyose



- Lymphome de Hodgkin (70 %)
- Causes bénignes : SIDA, lèpre, sarcoïdose pellagre; congénital

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Pyoderma (ecthyma) gangrenosum

- Hémopathies malignes
- Etiologies bénignes
- Dermatose neutrophilique: ulcération(s) extensive(s) limitée(s) par un bourrelet inflammatoire et pustuleux, d'évolution chronique

Syndrome des ongles jaunes (xanthonychie)

- Cancers bronchiques, maladies autoimmunes
- Coloration jaune des ongles, lymphoedème des MI

Syndrome de Weber Christian

- Adénocarcinomes pancréatiques, pancréatites
- Nodules sous-cutanés douloureux rouges violacés (aux faces d'extension des MI), évoluant vers le ramollissement et la fistulisation
- Fièvre, perte de poids

Vascularite leucocytoclasique

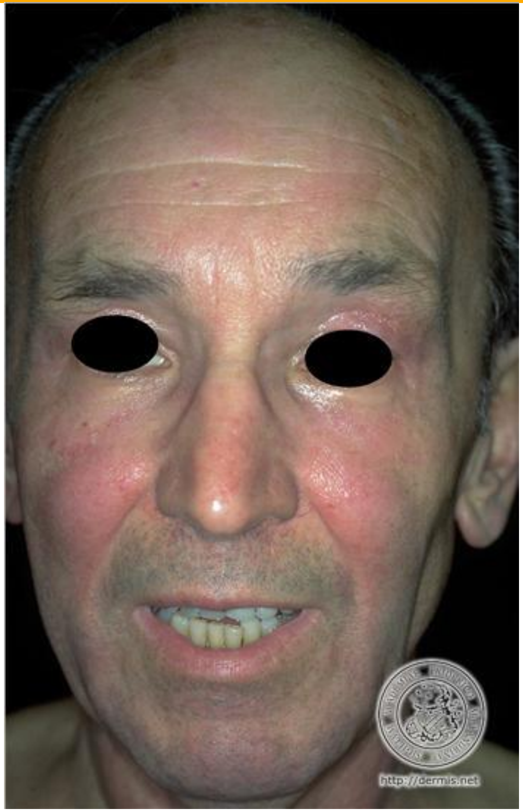
- Rare: hémopathies malignes > tumeurs solides
- Purpura palpable
- Purement cutanée dans 90 % des cas

Pemphigus paranéoplasique

LNH, LLC, thymome

(Dermato)polymyosite

- associées au cancer dans 15 à 25% des cas
- le risque de cancer dans cette affection est significativement accru.
- Principaux cancers concernés :
  ovaires > poumons > seins > pancréas> estomac> lymphome non hodgkinien.



érythème accompagné d'œdème des tissus sous-cutanés, tout particulièrement au niveau périorbitaire (violacé ou héliotrope avec œdème et télangiectasies des paupières), périoral, malaire, cervical antérieur, thoracique supérieure et surfaces d’extension

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Signe (papules) de Gottron

Auto-anticorps et myosites

→ Anticorps spécifiques de myosite (non exhaustif)

La présence d'anticorps spécifiques de myosite exclut en général l'origine paranéoplasique.

- **Antisynthétase** spécificité : amino-acyl-ARNt synthétase
  - Anti-Jo1 : histidyl-acyl-ARNt synthétase (le plus fréquent)
  - anti-PL7, -PL12 : thréonyl, alanyl-ARNt synthétase

  associés à un syndrome systémique spécifique (syndrome des antisynthétases)
- **Anti-SRP** spécificité : *signal recognition particle* (SRP)

  associé à une myopathie nécrosante auto-immune pure
- **Anti-Mi2, anti-PM-Scl**

→ Anticorps associés aux myosites

- **Anti-ribonucléoprotéine :** anti-Ro/SSA, anti-Ro52, anti-La/SSB
- **Anti-complexe ribonucléique :** anti-U1/RNP

TABLE 3. **Paraneoplastic Dermatologic and Rheumatologic Syndromes**[a]

Syndrome	Clinical presentation	Diagnostic studies/ laboratory findings	Associated cancers	Treatment options[b]
Acanthosis nigricans	Velvety, hyperpigmented skin (usually on flexural regions); papillomatous changes involving mucous membranes and mucocutaneous 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	Topical corticosteroids
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, nasopharyngeal	Prednisone, 80-100 mg/d orally Methylprednisolone, up to 1 g/d IV Azathioprine, up to 2.5 mg/kg/d orally Methotrexate, up to 25 mg/wk orally Cyclosporine A, 100-150 mg orally twice daily Mycophenolate mofetil, 2 g/d orally Cyclophosphamide, 0.5-1.0 g/m^2 IV IVIG, 400-1000 mg/d to total 2-3 g

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	Topical corticosteroids Narrow-band UVB phototherapy
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	NSAIDs Opiate analgesics Pamidronate, 90 mg IV Zoledronate, 4 mg IV Localized radiation therapy
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	Methylprednisolone, up to 1 g/d IV Prednisone, 1.0-1.5 mg/kg/d orally Dapsone, ~25-50 mg/d orally Colchicine, ~0.5 mg orally 2 or 3 times daily Methotrexate, 5-20 mg/wk orally Azathioprine, 0.5-2.5 mg/kg/d orally IVIG, 400-1000 mg/d to total 2-3 g

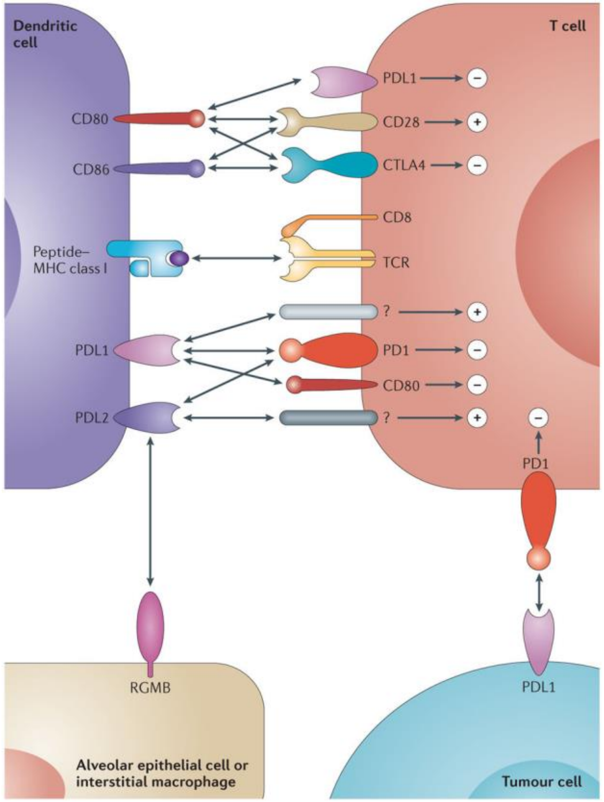
Syndrome	Clinical presentation	Diagnostic studies/ laboratory findings	Associated cancers	Treatment options[b]
Paraneoplastic pemphigus (PNP)	Severe cutaneous blisters and and erosions (predominantly on trunk, soles, palms); severe mucosal erosions, including stomatitis	Serum antibodies to epithelia (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	Prednisone, ~60-120 mg orally daily Azathioprine, ~1.5 mg/kg/d orally Cyclophosphamide, 100-150 mg/d orally Cyclosporine A (target plasma levels 100-150 ng/L) IVIG, 400-1000 mg/d to total 2-3 g Mycophenolate mofetil, 1-2 g/d orally Plasma exchange Rituximab, 375 mg/m^2 IV per dose
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	Prednisone, ~15 mg/d orally Methotrexate, ~10 mg/wk orally
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	Clobetasol propionate, 0.05% topical Triamcinolone acetonide, 3-10 mg/mL intralesional injection(s) Methylprednisolone, up to 1 g/d IV Prednisone, 30-60 mg/d orally Potassium iodide, 300 mg orally 3 times daily (tablets) or 1050-1500 mg/d orally of saturated solution (Lugol solution) Colchicine, ~0.5 mg orally 3 times daily

TABLE 4. **Paraneoplastic Hematologic Syndromes**[a]

Syndrome	Clinical presentation	Laboratory findings	Associated cancers	Treatment options[b]
Eosinophilia	Dyspnea, wheezing	Hypereosinophilia ($>0.5 \times 10^9$/L); elevated serum IL-5, IL-3, IL-2 and GM-CSF	Hodgkin lymphoma, non-Hodgkin lymphoma (B- and T-cell), chronic myeloid leukemia, acute lymphocytic leukemia, lung, thyroid, GI (pancreatic, colon, gastric, liver), renal, breast, gynecologic	Inhaled corticosteroids Prednisone, 1 mg/kg/d orally
Granulocytosis	Asymptomatic (no symptoms or signs of leukostasis such as neurologic deficits or dyspnea)	Granulocyte (neutrophil) count $>8 \times 10^9$/L, typically without a shift to immature neutrophil forms; elevated LAP; elevated serum G-CSF	GI, lung, breast, gynecologic, GU, brain, Hodgkin lymphoma, sarcomas	Specific treatment not indicated
Pure red cell aplasia	Dyspnea, pallor, fatigue, syncope	Anemia (hematocrit, <20 not uncommon), low/absent reticulocytes, bone marrow with nearly absent erythroid precursors, platelet and white blood cell counts in normal ranges	Thymoma, leukemia/lymphoma, myelodysplastic syndrome	Blood transfusions Prednisone, 1 mg/kg/d orally Antithymocyte globulin, 500 mg daily IV (with corticosteroids and/or cyclophosphamide) Cyclosporine A, 100 mg orally twice daily Cyclophosphamide, 1-3 mg/kg/d orally Rituximab, 375 mg/m^2 IV per dose Alemtuzumab, 30 mg IV per dose Plasma exchange Splenectomy
Thrombocytosis	Asymptomatic (no bleeding or clotting abnormalities)	Elevated platelet count, greater than $\sim 400 \times 10^9$/L; elevated serum IL-6	GI, lung, breast, gynecologic, lymphoma, renal cell, prostate, mesothelioma, glioblastoma, head and neck	Specific treatment not indicated

Quoi de neuf en 2017?

- Complications des nouvelles immunothérapies (inhibiteurs des points de contrôle)



Nature Reviews | Immunology

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Review European Journal of Cancer 82 (2017) 128–136

Myasthenia gravis: An emerging toxicity of immune checkpoint inhibitors

D. Makarious [a], K. Horwood [b], J.I.G. Coward [b,c,d,*]

PD-1 Checkpoint Inhibitor Associated Autoimmune Encephalitis

Case Rep Oncol 2017;10:473–478

Stephanie Schneider[a] Silke Potthast[b] Paul Komminoth[c]
Guido Schwegler[d] Steffen Böhm[a]

JAMA Neurology | Original Investigation *JAMA Neurol*. 2016;73(8):928-933.

Association of Autoimmune Encephalitis With Combined Immune Checkpoint Inhibitor Treatment for Metastatic Cancer

Tanya J. Williams, MD, PhD; David R. Benavides, MD, PhD; Kelly-Ann Patrice, MBBS; Josep O. Dalmau, MD, PhD; Alexandre Leon Ribeiro de Ávila, MD, PhD; Dung T. Le, MD; Evan J. Lipson, MD; John C. Probasco, MD; Ellen M. Mowry, MD, MCR

Nivolumab-induced myasthenia gravis in a patient with squamous cell lung carcinoma

Case report

Medicine (2017) 96:27(e7350)

Yu-Hsiu Chen, MD[a], Feng-Cheng Liu, MD, PhD[a], Chang-Hung Hsu, MD[b], Chih-Feng Chian, MD[c,*]

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www.oncorea.com

www.pneumocancero.com

Autoimmune paraneoplastic syndromes associated to lung cancer: A systematic review of the literature

Valérie Durieux[a], Michelle Coureau[b], Anne-Pascale Meert[b], Thierry Berghmans[b], Jean-Paul Sculier[b,*]

Lung Cancer 106 (2017) 102–109

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