Cutaneous, renal and neurological manifestations of plasma cell dyscrasias

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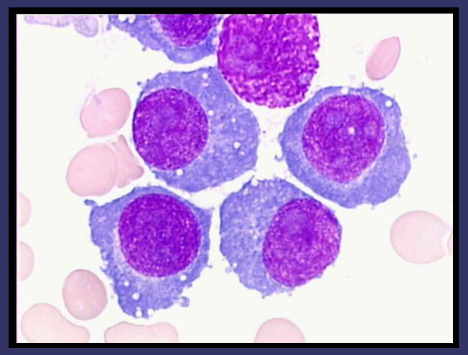
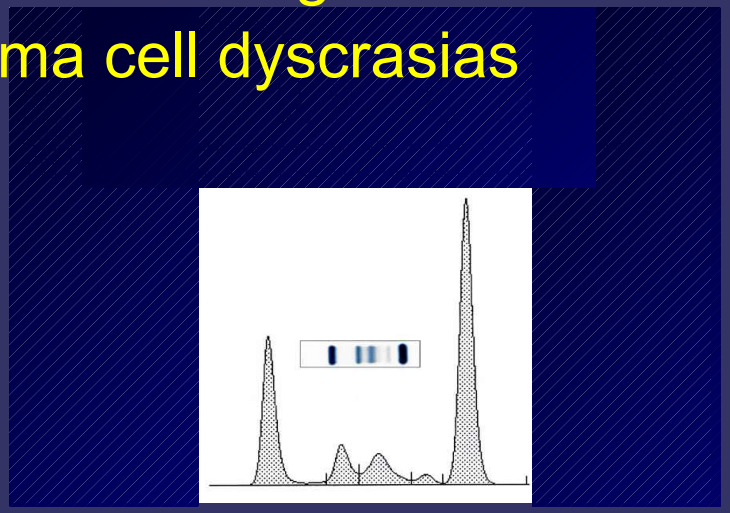
Cutaneous, renal and neurological manifestations of plasma cell dyscrasias



Clonal B cells



Monoclonal immunoglobulin (MIg)

1) Related to clonal cells

2) Related to MIg

3) Still poorly understood pathogenesis

The skin

Cutaneous manifestations and gammopathies

1) Related to clonal cells

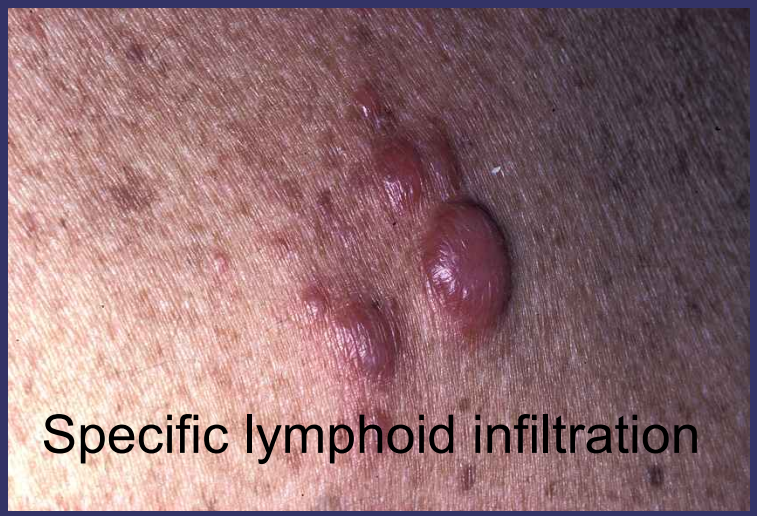
- direct lympho and/or plasmocytoid infiltration

- adsorption to malignant cells

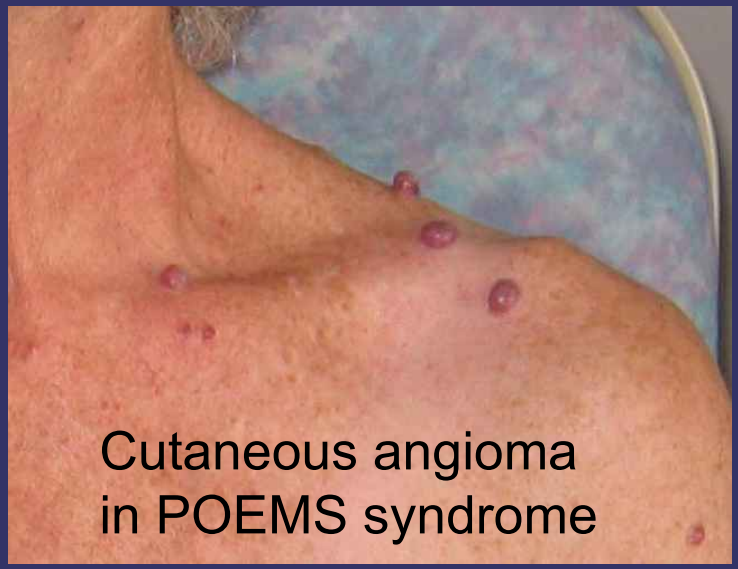
  von Willebrand syndrome, acquired angioedema (?)

- abnormal cytokine secretion

  by the clonal cells or their environment



Specific lymphoid infiltration



Cutaneous angioma
in POEMS syndrome

Cutaneous manifestations and gammopathies

2) Related to MIg

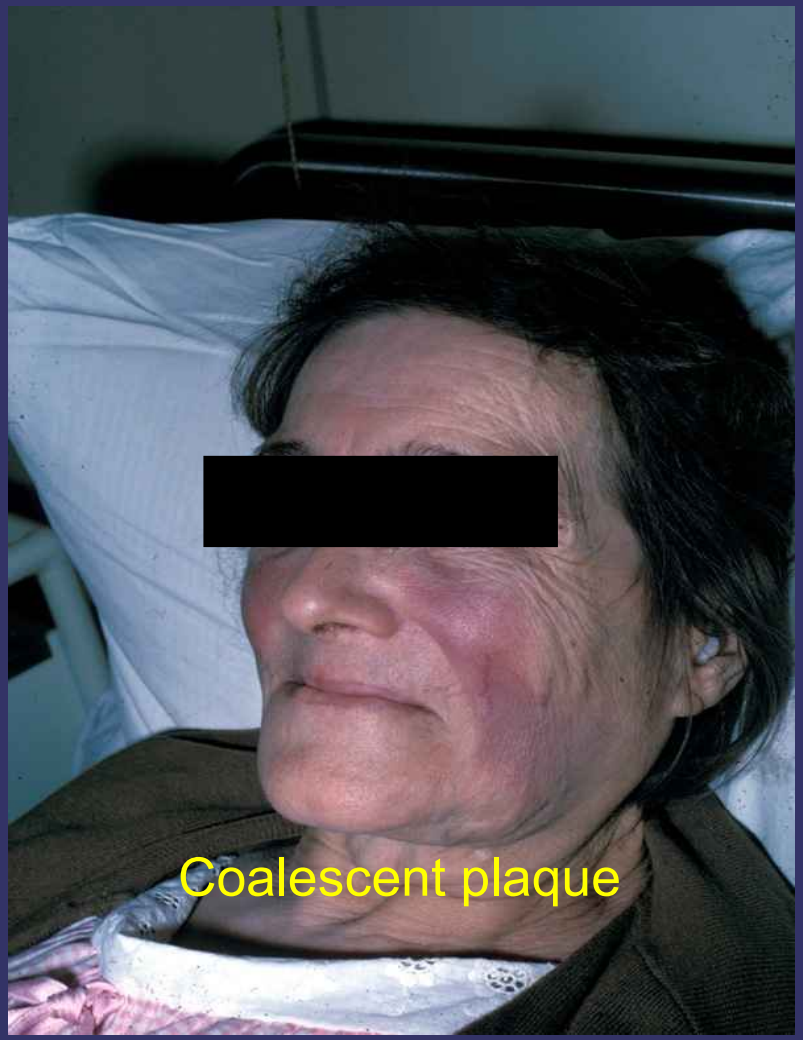
high concentration: hyper viscosity

Specific physico-chemical properties

deposition

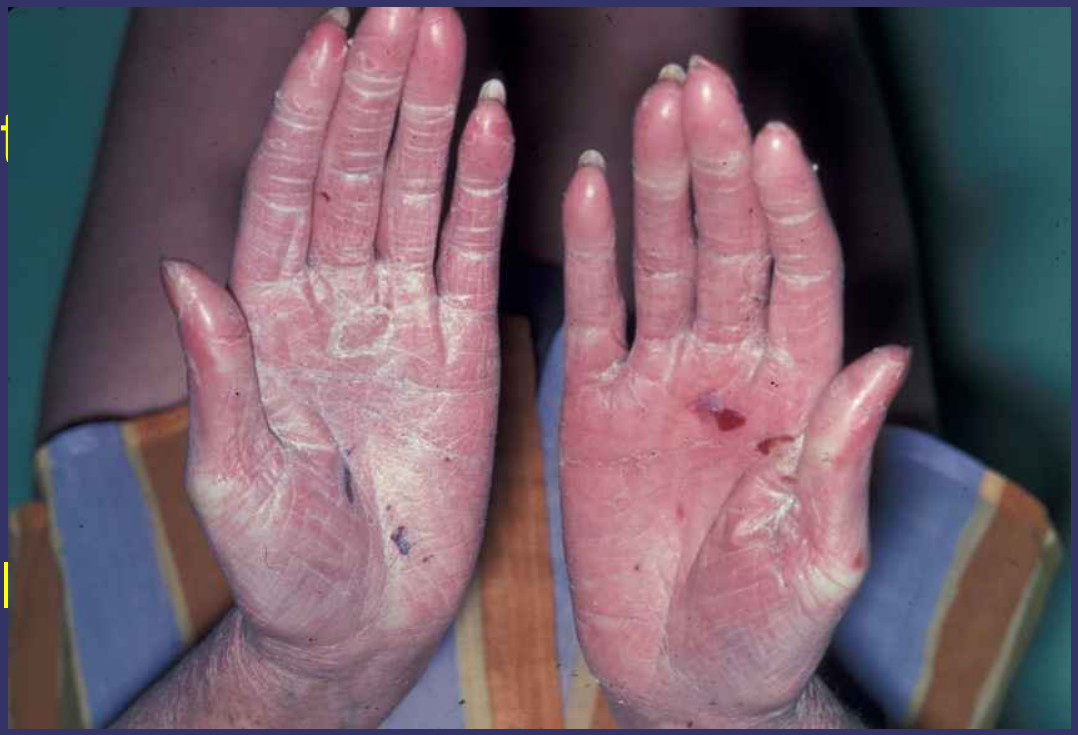
- *along basal membranes: MIg deposition disease*
- *within the dermis (« Ig storage papules»)*

IgM storage papules: cutaneous macroglobulinosis



(Personal data & Lipsker et al, B.J.Dermatol, 1996)

Cutaneous manifest



2) Related to MIg

high concentration

Specific physico-chemical

deposition

- along basal membranes: *MIg deposition disease*
- within the dermis *(« Ig storage papules»)*

aggregation

* fibrils *(AL amyloidosis),*
* crystals *(crystal-storing histiocytosis)*
* microtubules *(type I cryoglobulinemia)*

Cutaneous manifestations and gammopathies

2) Related to MIg

High concentration

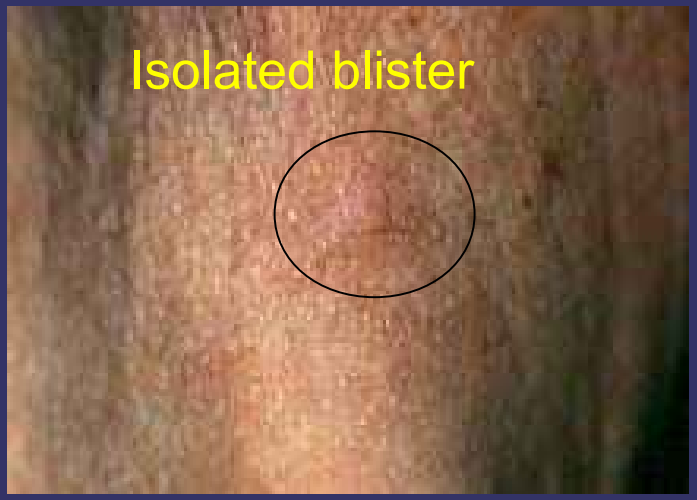
specific physico-chemical properties

auto-antibody activity

- directed to a cutaneous component (usually collagen VII):

bullous skin diseases

Post blistering erosions



Aractingi & Fermand, 1999, Medicine

Cutaneous manifestations and gammopathies

2) Related to MIg

High concentration

Specific physico-chemical properties

Auto-antibody activity

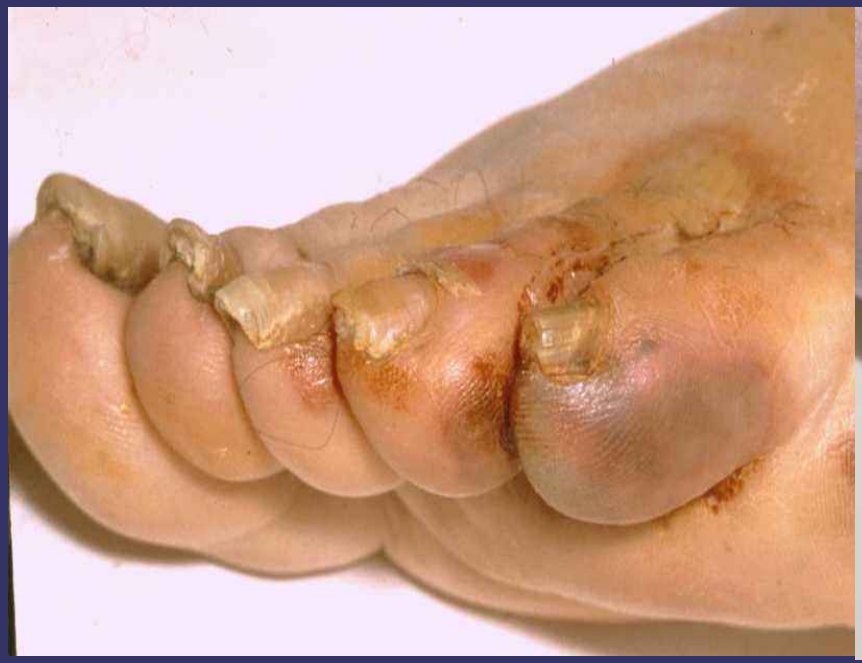
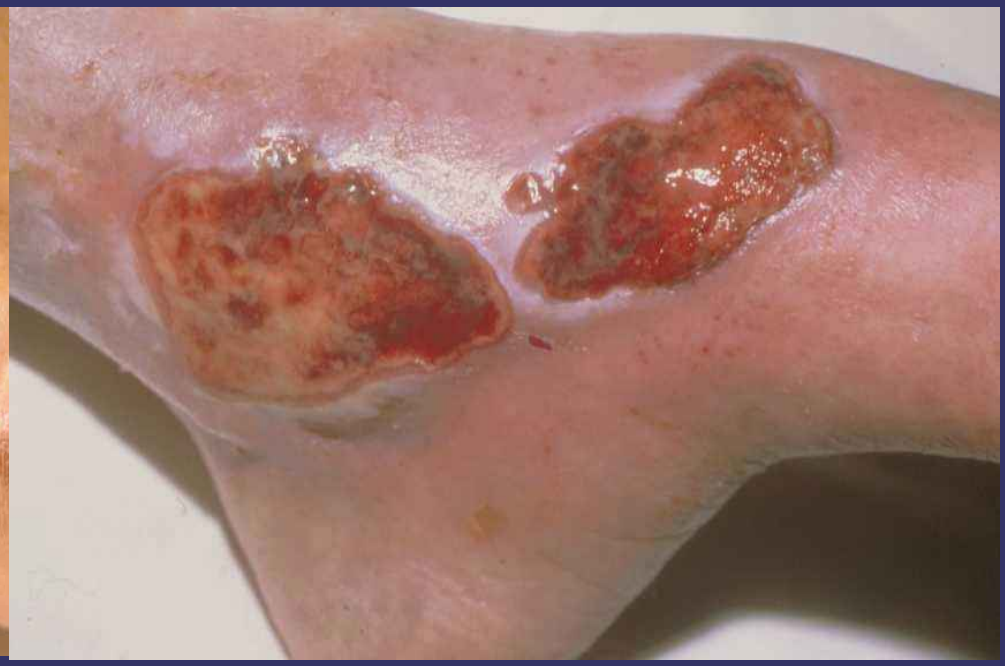
- directed to a cutaneous component
- immune complex mediated:

* intra-vascular precipitation/ vasculitis:

cold agglutinin disease,

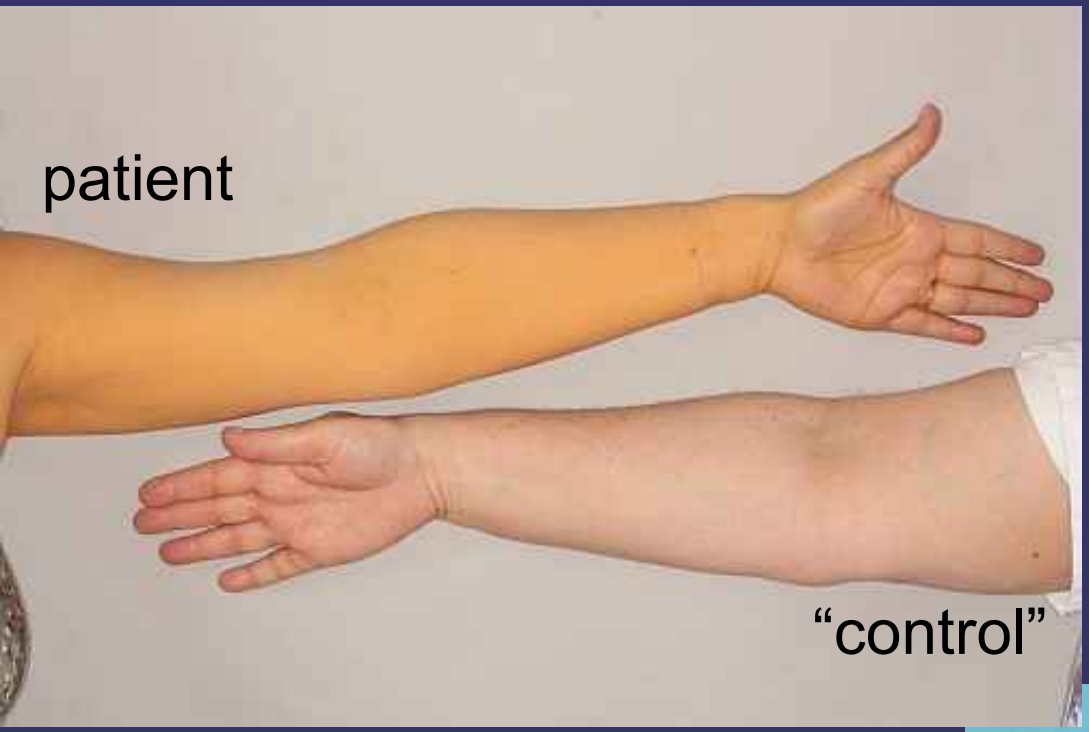
type II mixed cryoglobulinemia

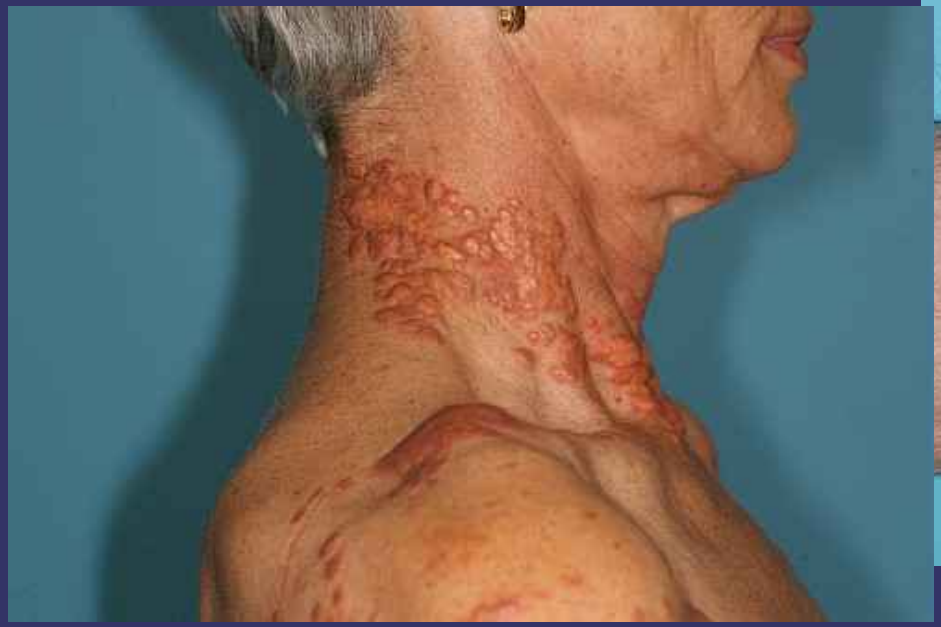
* intra-cellular storage: *xanthomatosis*

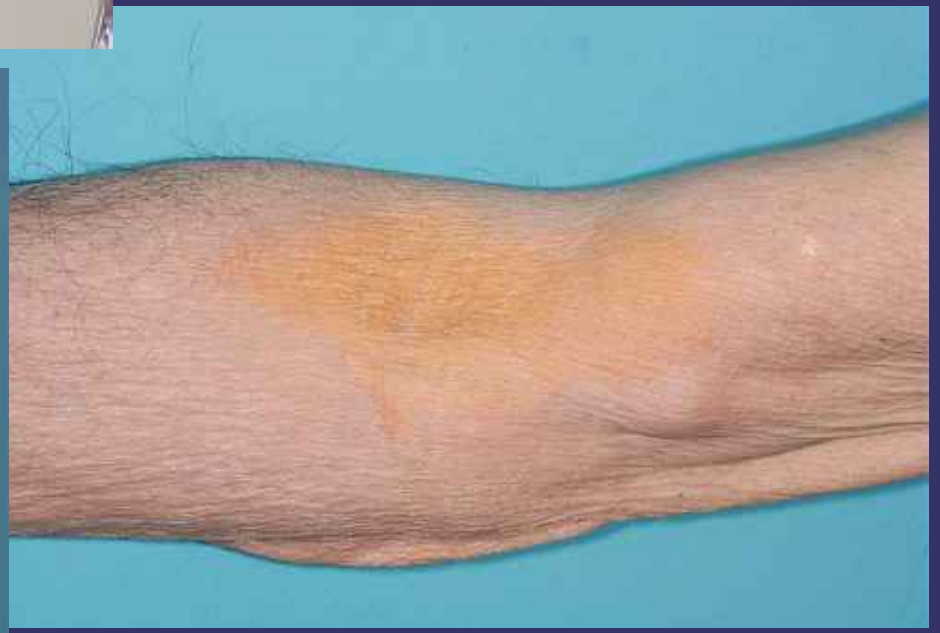



Ischemic and ulcerous lesions due to type II cryoglobulinemia

Xanthomas and MIg





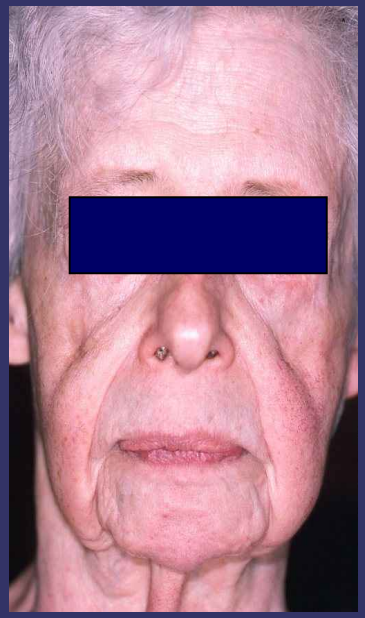


Cutaneous manifestations and gam

3) still poorly understood pathogenesis

Neutrophilic dermatoses

Oedematous red plaque of Sweet's Syndrome



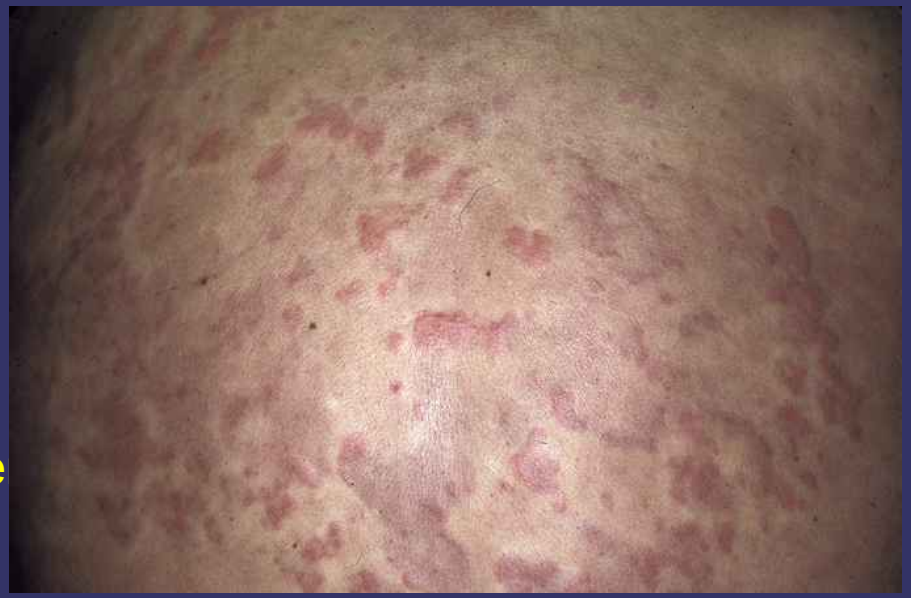
Cutaneous mucinosis
(papular mucinosis, scleromyxoedema)

papular mucinosis

Acquired cutis laxa

Schnitzler syndrome

Schnitzler syndrome



Recurrent urticarial rash

+ Monoclonal IgM (κ: 9/10)

usually at low level, without ove

MW

± intermittent fever, fatigue, weight loss

± articular, musculoskeletal
and/or bone manifestations

histoimmunopathology : mild dermal perivascular neutrophilic infiltration,
Ig or C' deposits # 30%

Hyperleucocytosis, Inflammatory syndrome

↗ ESR, CRP & fibrin, anemia & thrombocytosis, hypoalbuminemia

Treatment: - steroids # always effective on urticaria and fever but corticodependance

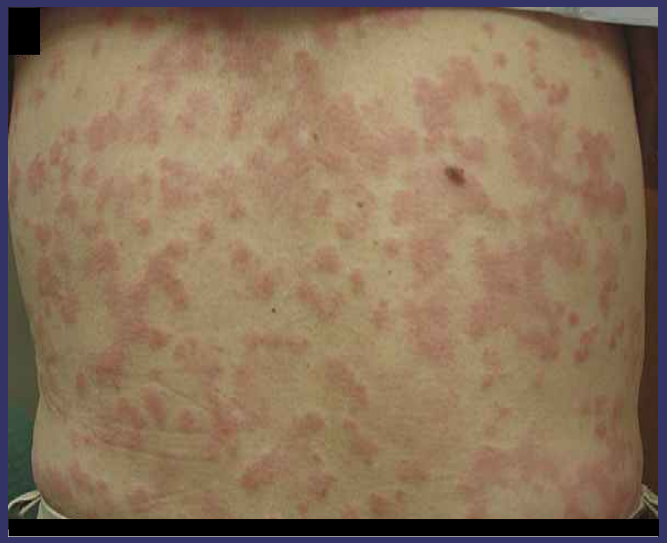
(precise threshold dosage (10-30 mg/d))

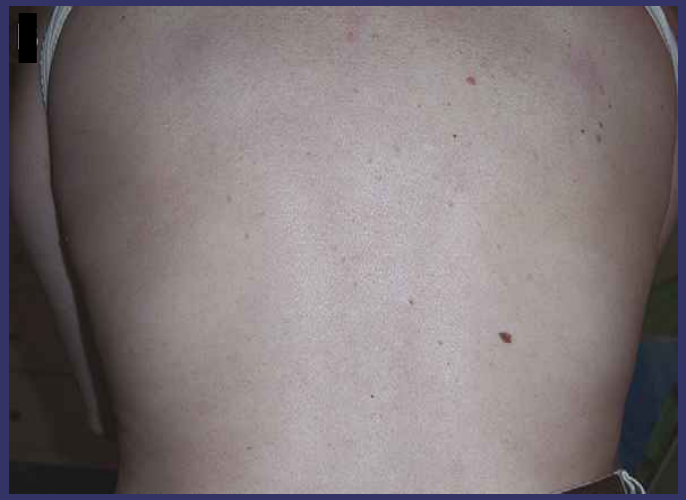
- Thalidomide, α-interferon: effective but tolerability issues
- symptomatic efficacy of the antibiotic pefloxacin

Schnitzler syndrome: Efficacy of IL-1 receptor antagonist

(Anakinra (Kineret*) 100 mg/day SC)

n= 23 (literature 15, Saint Louis 8)





Dramatic and complete improvement in urticaria, fever and bone pain

Normalization of all other biologic abnormalities (C-reactive protein, Hb, leukocyte and platelet counts)

No effect on MIg level

Tapering/cessation of steroids

Sustained but symptomatic efficacy well tolerated

Schnitzler syndrome

= acquired auto-inflammatory syndrome?

unregulated secretion of IL-1 via interaction of a clonal product (the MIg?) with a key component of the IL1 pathway?

Genetic “auto-inflammatory” diseases

Familial cold autoinflammatory syndrome (FCAS),

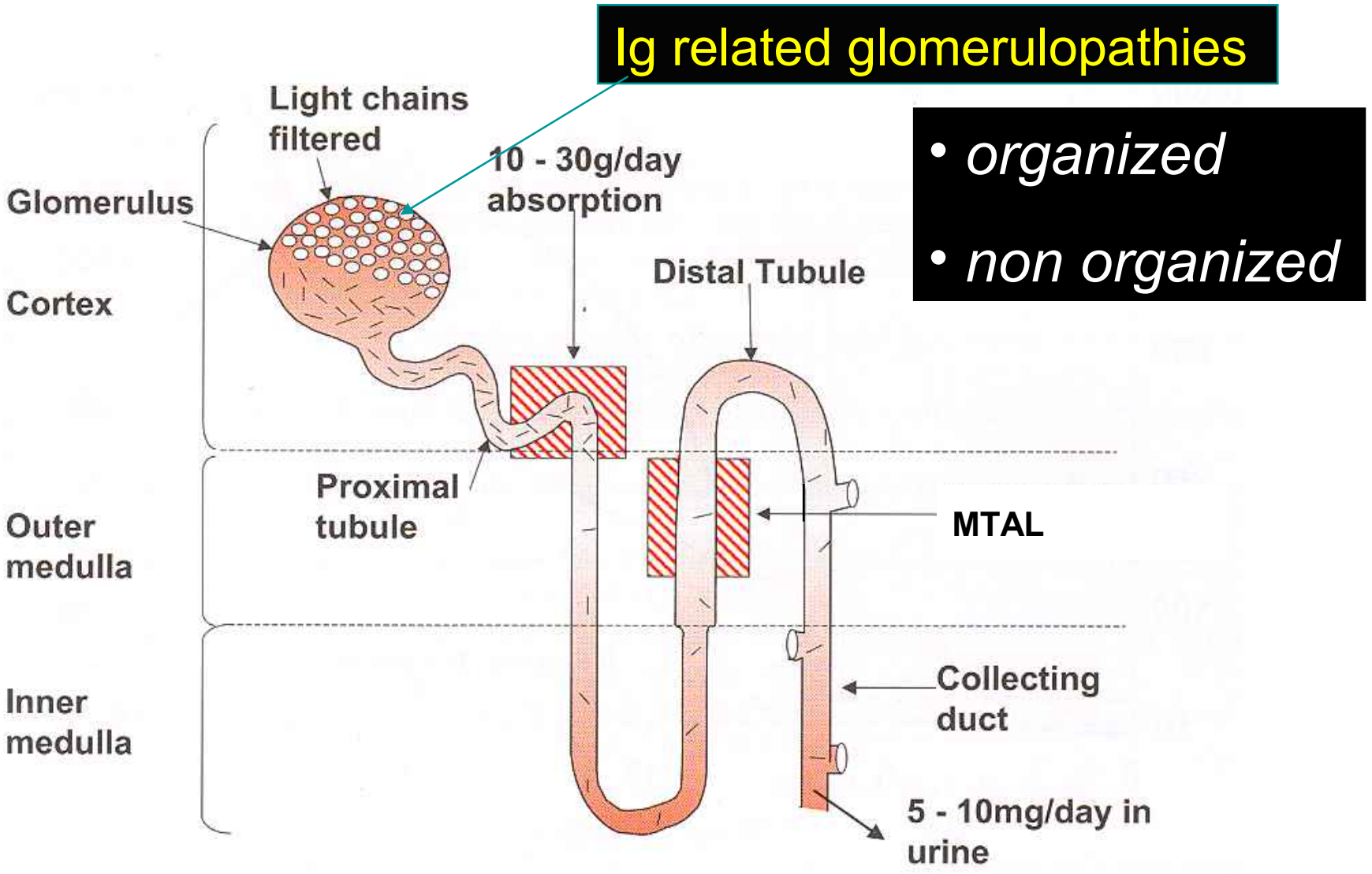
Muckle Wells syndrome (MWS) ….

due to mutations in intra-cellular NOD-like receptors (cryopyrin)

= skin rashes and periodic fever

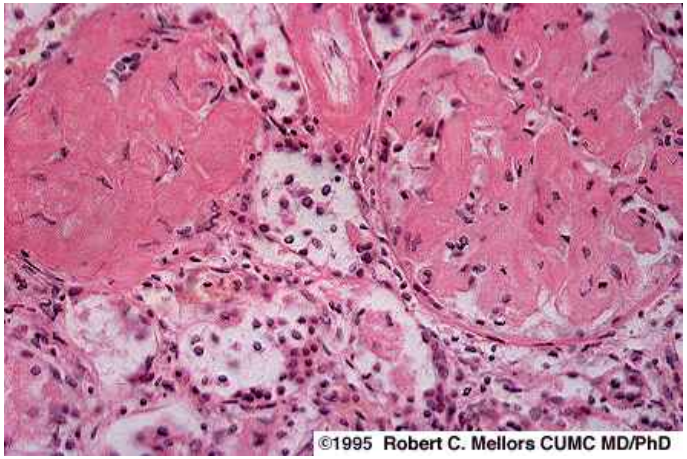
The Kidney

renal metabolism of Ig light chains (LC)



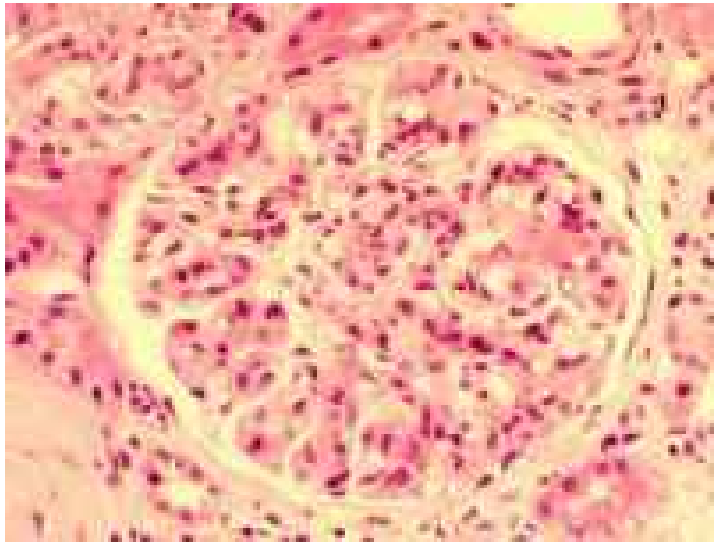
Monoclonal immunoglobulin (Ig) related nephropathies: Glomerulopathies

organized deposits *(electronic microscopy):*



Fibrillar:

AL(AH) Amyloïdosis



Microtubular:

type I and II cryoglobulinemia

GOMMID (GN with organized microtubular monoclonal Ig deposits) or «immunotactoïd» GN

Monoclonal immunoglobulin (Ig) related nephropathies: Glomerulopathies

Organized deposits *(electronic microscopy)*

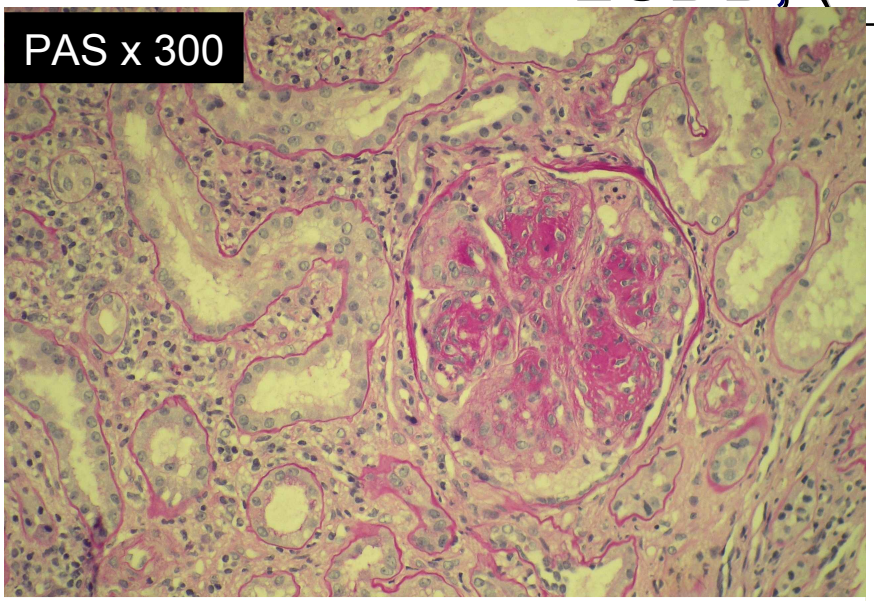
Non-organized deposits *(amorphous and granular)* :

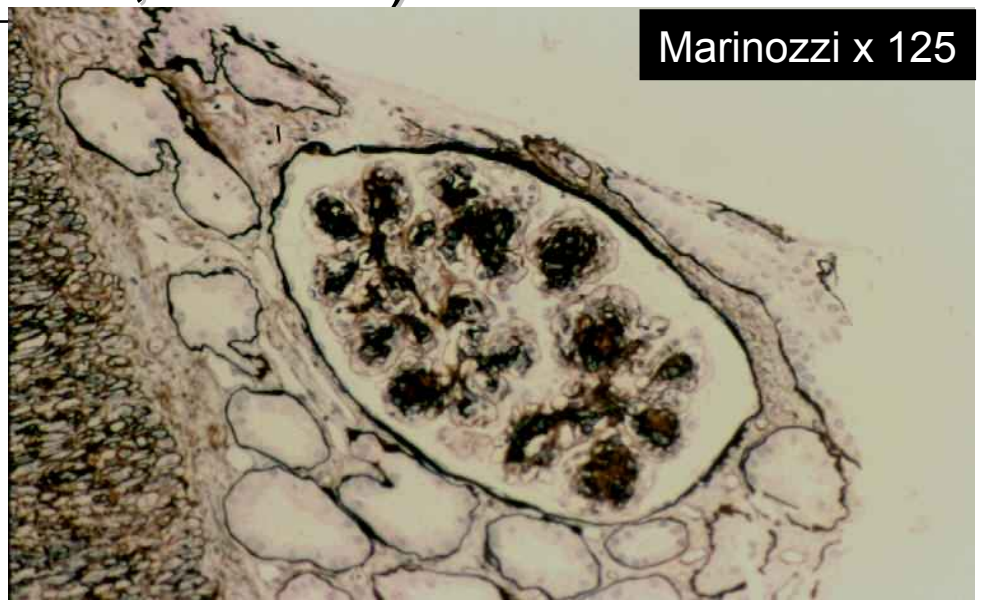
MIDD (monoclonal Ig deposition disease
or Randall's diseases) : LCDD, HCDD, LHCDD

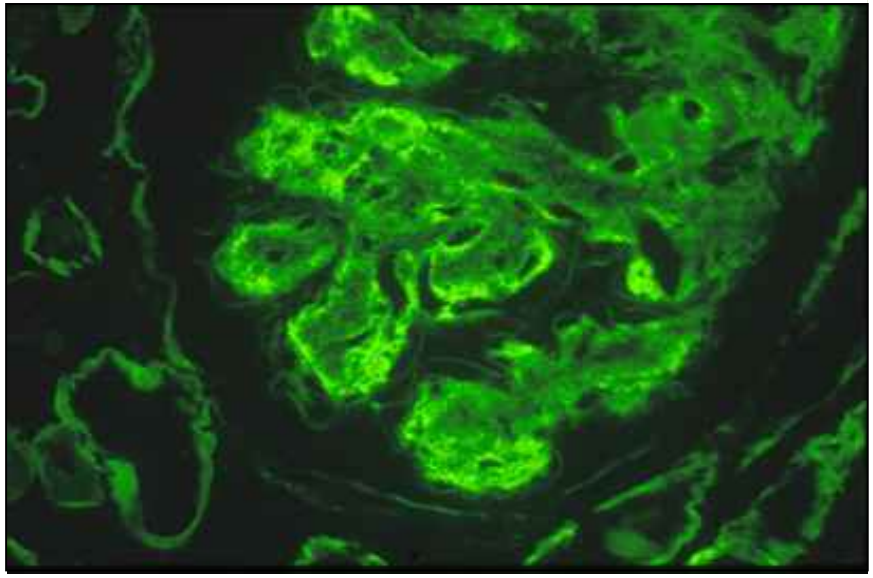
Other

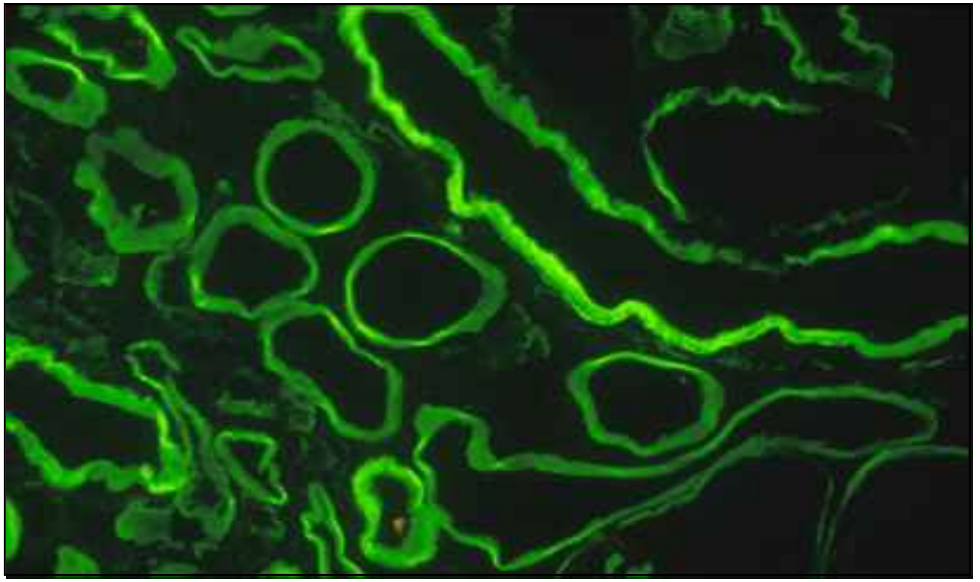
Non-organized Randall-type deposits

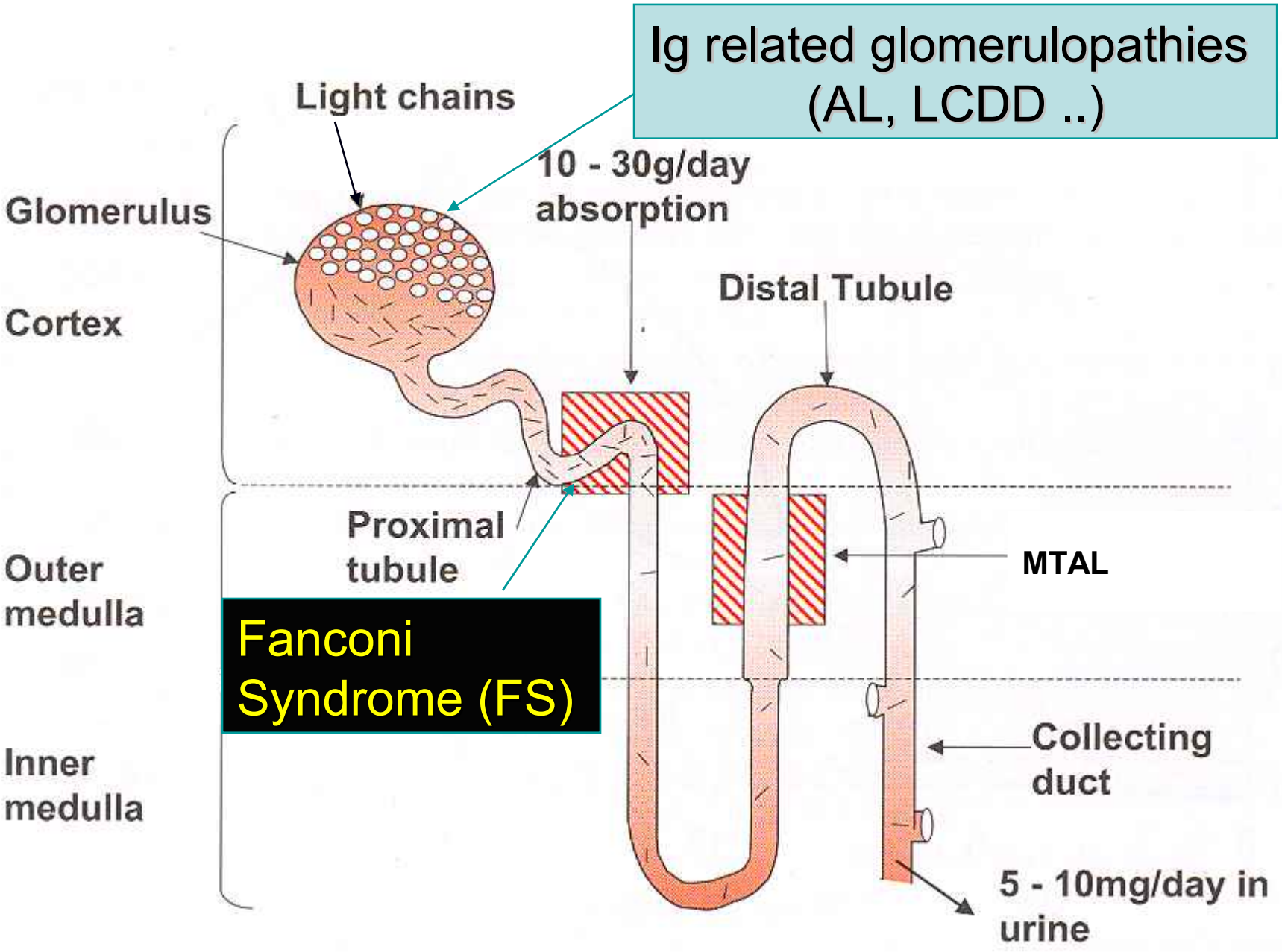
LCDD, (HCDD, LHCDD)

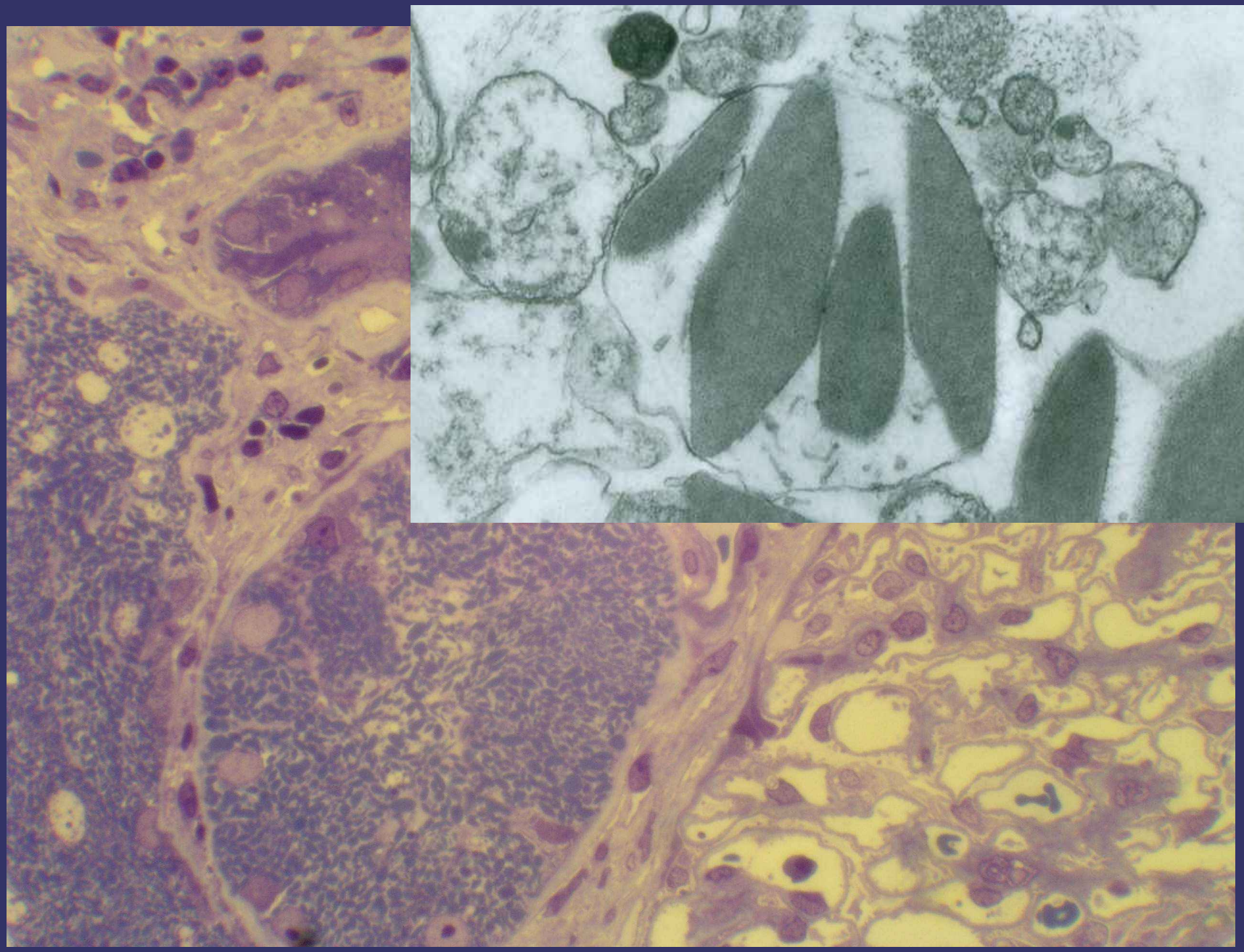






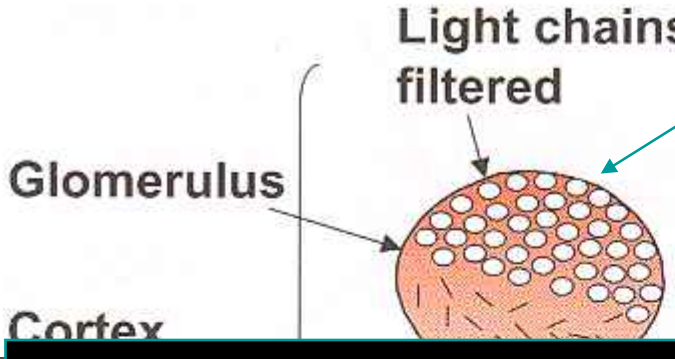



Ig related glomerulopathies (AL, LCDD ..)
Light chains
10 - 30g/day absorption
Glomerulus
Cortex
Distal Tubule
Proximal tubule
MTAL
Outer medulla
Fanconi Syndrome (FS)
Inner medulla
Collecting duct
5 - 10mg/day in urine

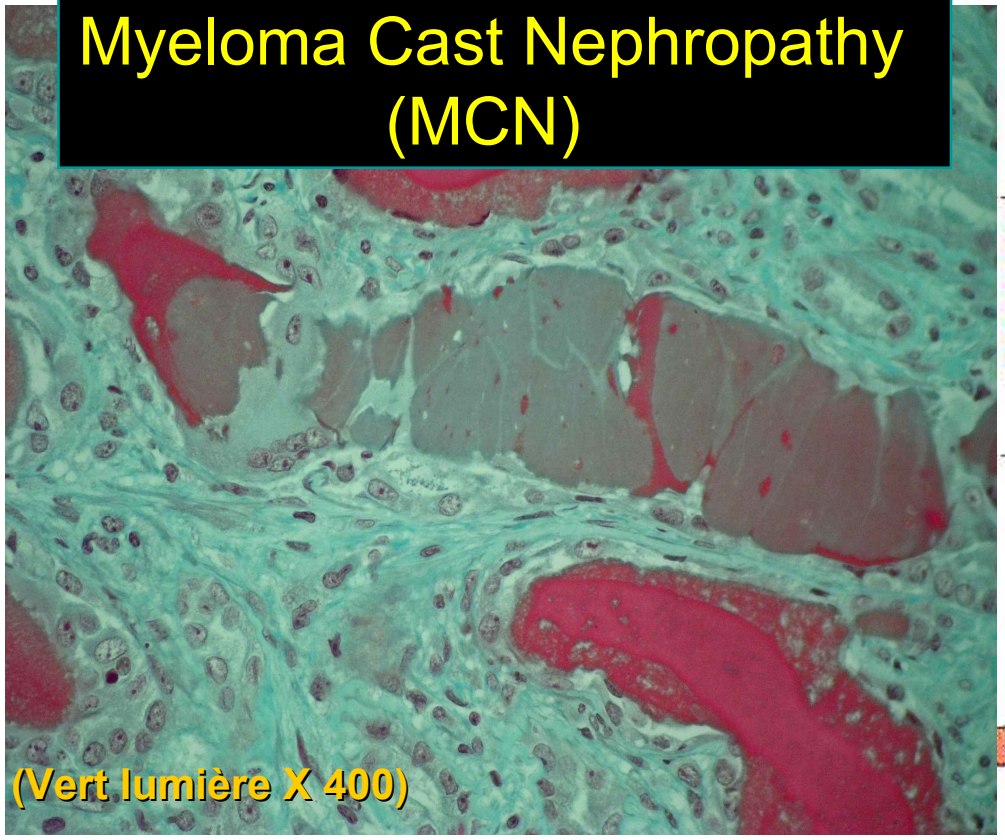


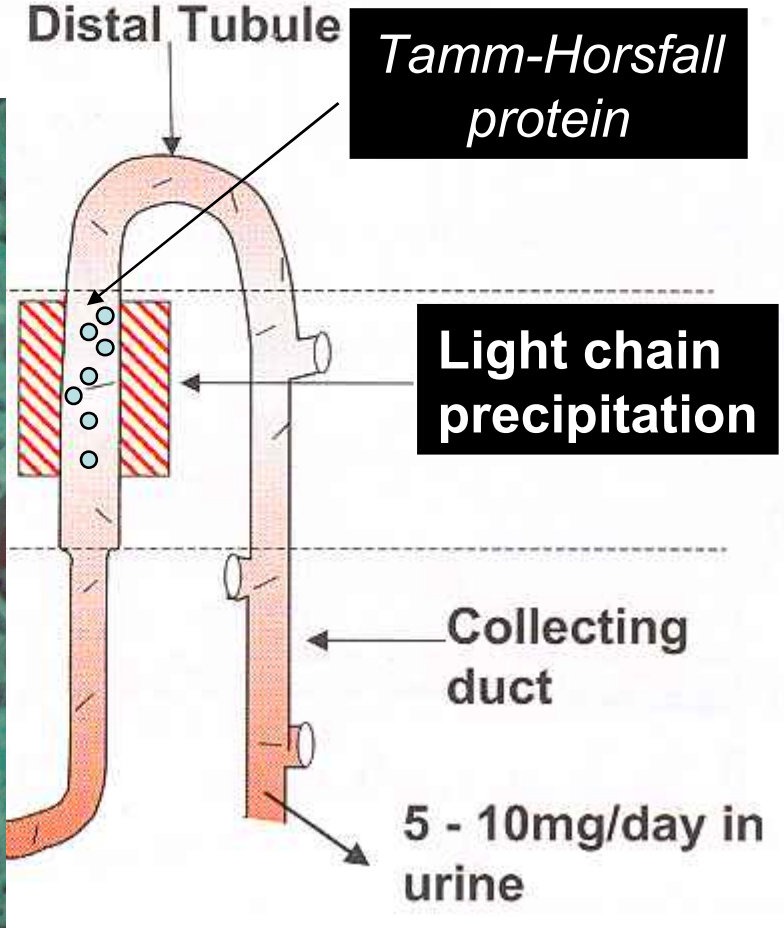
Bleu de Toluidine X 1.000

Ig related glomerulopathies (AL, LCDD ..)



Myeloma Cast Nephropathy (MCN)





Renal impairment and monoclonal Ig : glomerulopathy or tubulopathy?

Key component of proteinuria?

If albuminuria > 1g/d → Ig glomerular deposits? → Which kind?

other renal features

extra-renal symptoms

characteristics of the monoclonal gammopathy

AL amyloido

proteinuria ± ne
frequent extra-r
MGUS or stage

L(H)C deposition disease

proteinuria ± nephrotic syndrome,
hematuria, hypertension, renal failure
± extra-renal symptoms
overt MM, $\kappa > \lambda$

Non-organized Randall-type deposits: LCDD, (HCDD, LHCDD)

mean age # 55 yrs,

prominent renal manifestations :

- proteinuria (> 1 g/d : 75 %) ± nephrotic syndrome
- hypertension (#50 %)
- microscopic hematuria (30-60 %)
- renal failure > 90 %
- symptoms of chronic interstitial nephritis (25%)

± extra renal deposits:

- basement membranes of most tissues
  - liver (involvement virtually constant by IF), heart, ….

overt MM # 50%, “primary” forms # 50%,

CLL, WM & B-cell lymphoma exceptional

- detectable serum and/or urine monoclonal component : 70- 95 %
- κ isotype # 65%

LCDD : over-representation of the VkIV subgroup

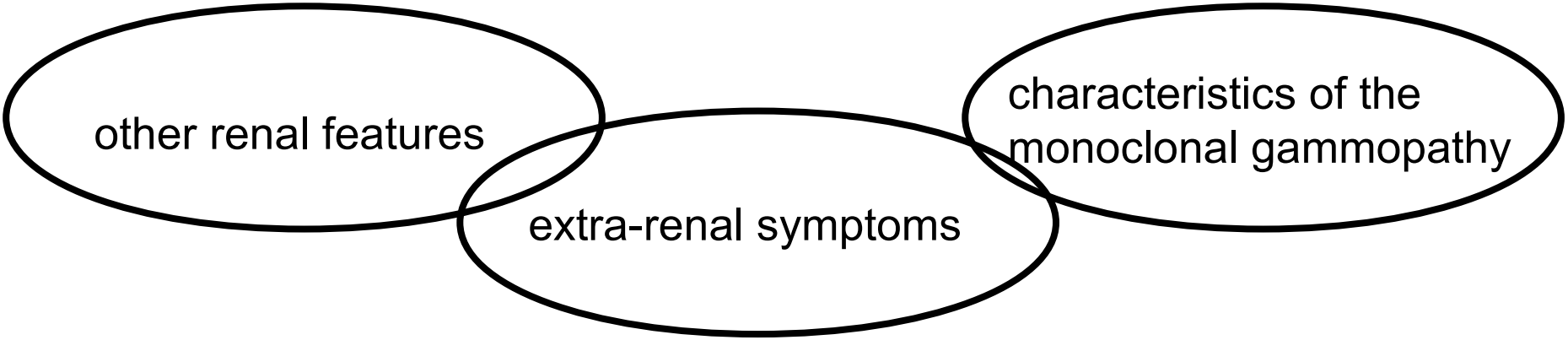
HCDD (rare): systematic deletion of CH1

- circulating truncated HC, either alone or associated with LC
- frequent serum complement activation

Renal impairment and monoclonal Ig : glomerulopathy or tubulopathy?

Key component of proteinuria?

If albuminuria > 1g/d → Ig glomerular deposits? → Which kind?



AL amyloidos

proteinuria
frequent extra-re
MGUS or stage

L(H)C deposit

hematuria, hypert
± extra-renal sym
overt MM, κ>λ

cryoglobulinemia

suggestive extra-renal sy
purpura)
Type I or type II cryoglob

extra-renal biopsy and/or histologic renal examination

Renal impairment and monoclonal Ig : glomerulopathy or tubulopathy?

Key component of proteinuria?

If LC > 70%, albuminuria < 1g/d

Fanconi syndrome

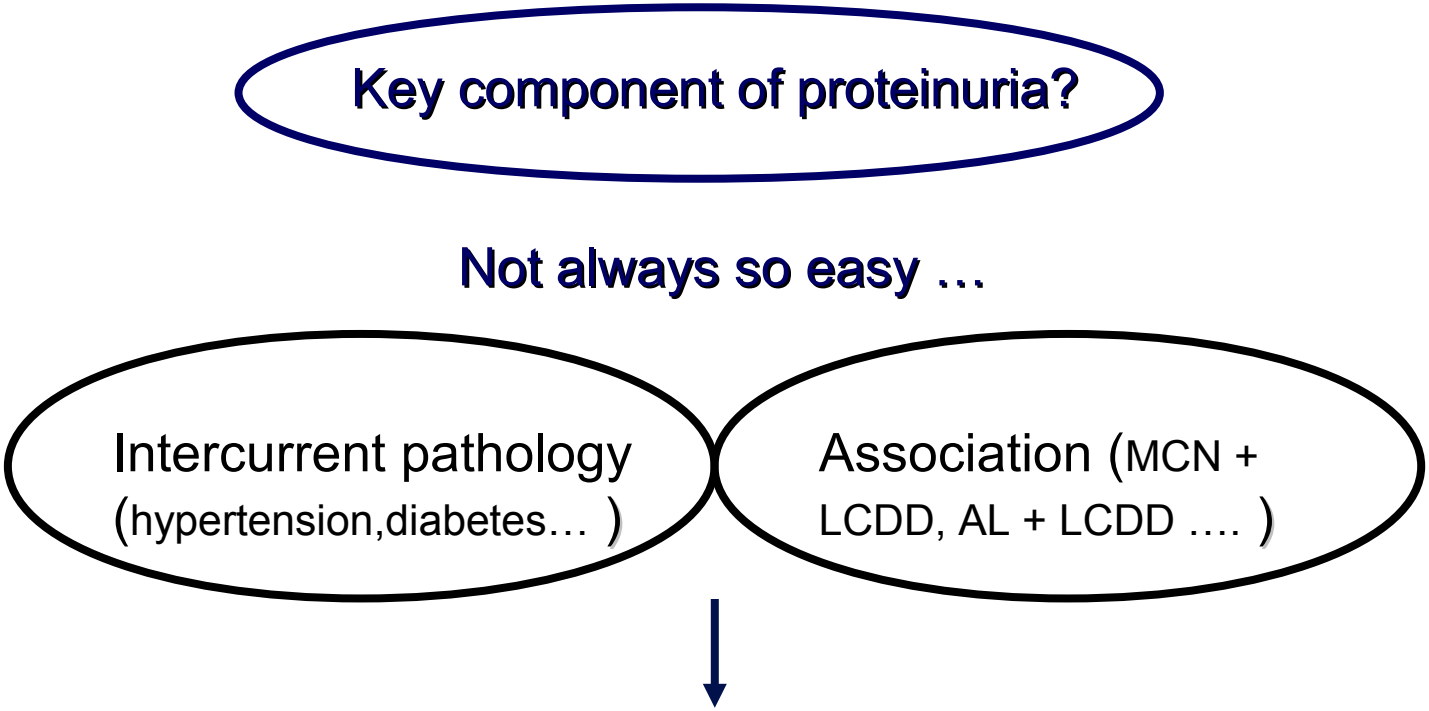
always κ LC ± mild chronic renal failure

Proximal tubular abnormalities

hypouricemia, hypophosphatemia, hypokaliemia, aminoaciduria, glycosuria without hyperglycemia, LMW proteinuria, hypercalciuria

Myeloma cast nephropathy

Renal impairment and monoclonal Ig : glomerulopathy or tubulopathy?



Randall-type MIDD: Treatment

Conventional chemotherapy (MP, VAD, VAMP)

- Median renal survival ~ 2 years
- Median patient survival ~ 4 years

High dose chemotherapy and autotransplantation

- low treatment related mortality (≠ AL)
- frequent improvement in the function of involved organs

  * including withdrawal of chronic haemodialysis in some case

Novel anti-myeloma agents (bortezomib)

Kidney transplantation

- after (high-dose) chemo to reduce LC(HC) production
- carefully monitoring LC(HC) levels
- frequent recurrence

  (median time post transplant # 3 yrs, back to haemodialysis # 4 yr)

The peripheral nerve

Peripheral neuropathy and monoclonal Ig

in all cases

- direct lympho and/or plasmocytoid infiltration

- Ig deposits (AL amyloidosis, Ig deposition disease)
- intra-vascular precipitation/ vasculitis (type II cryoglobulinemia)

- drug neurotoxicity

monoclonal IgM

- auto-antibody activity

monoclonal IgG, IgA or LC only

- POEMS syndrome

Peripheral neuropathy (PN) and monoclonal IgM

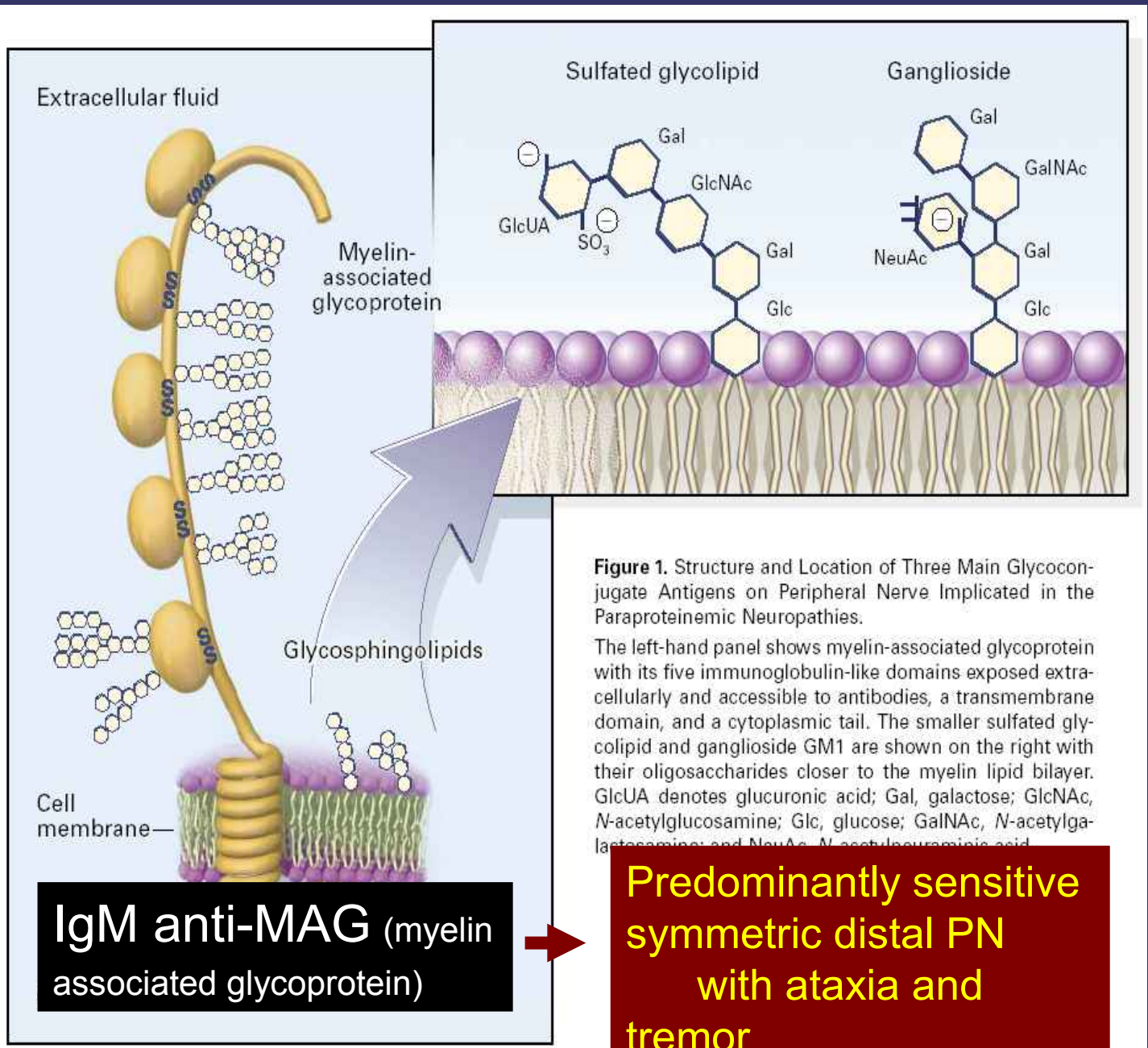


Figure 1. Structure and Location of Three Main Glycoconjugate Antigens on Peripheral Nerve Implicated in the Paraproteinemic Neuropathies.

The left-hand panel shows myelin-associated glycoprotein with its five immunoglobulin-like domains exposed extracellularly and accessible to antibodies, a transmembrane domain, and a cytoplasmic tail. The smaller sulfated glycolipid and ganglioside GM1 are shown on the right with their oligosaccharides closer to the myelin lipid bilayer. GlcUA denotes glucuronic acid; Gal, galactose; GlcNAc, *N*-acetylglucosamine; Glc, glucose; GalNAc, *N*-acetylga-

IgM anti-MAG (myelin associated glycoprotein)

Predominantly sensitive symmetric distal PN with ataxia and tremor

Peripheral neuropathy (PN) and monoclonal IgM

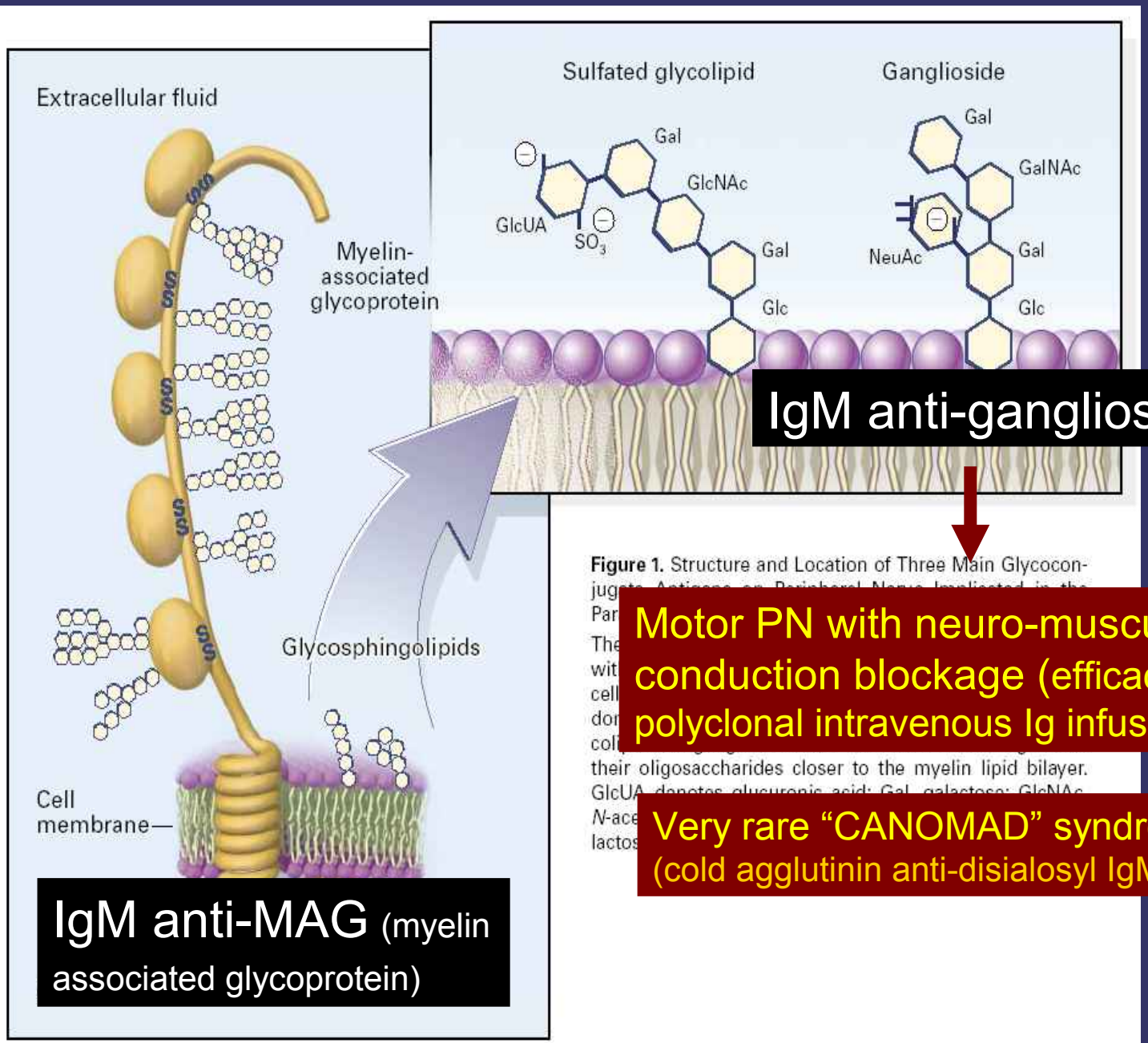


Figure 1. Structure and Location of Three Main Glycocon-
jug
Par
The
wit
cell
dor
col
their oligosaccharides closer to the myelin lipid bilayer.
GlcUA
N-ace
lactos

Peripheral neuropathy and monoclonal IgG/A

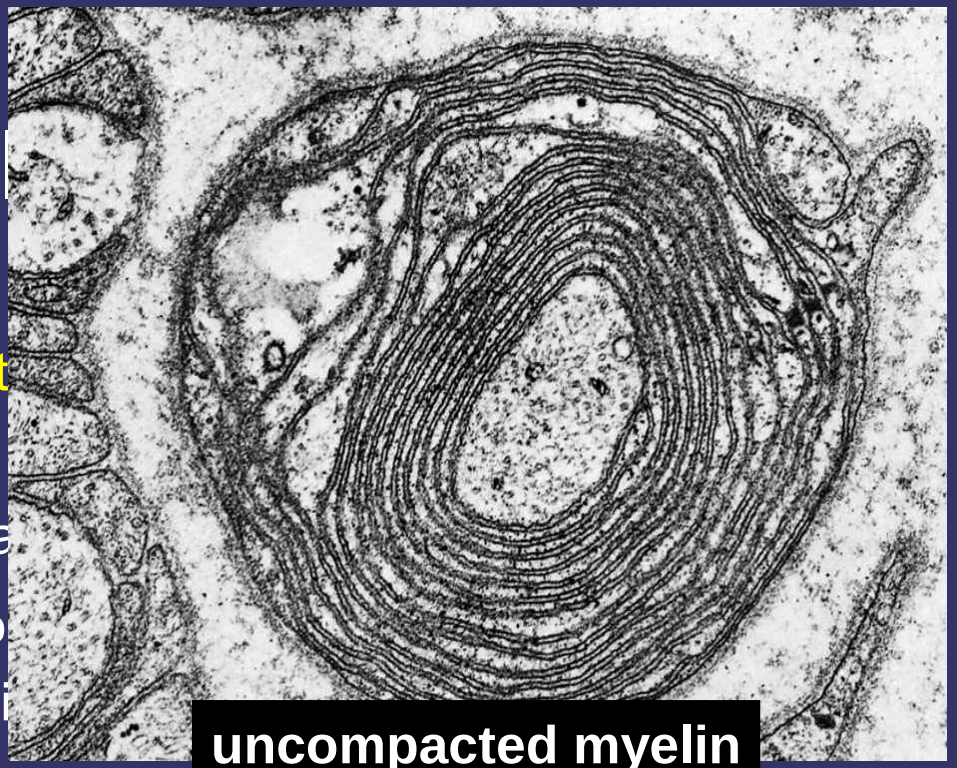
POEMS syndrome

- Polyneuropathy
- Organomegaly
- Endocrinopathy
- Monoclonal gammopathy
- Skin changes

rare (<1/100 myeloma), Asie > Europe/U.S.

mean age # 50 yrs, M/F 2/1

POEMS : po



- 100 % (No POEMS without neuropat
- Usually first and prominent manifesta
- Sensory symptoms preceeding moto
  distal, symmetric and progressive, wi
- Severe weakness (>50%) → inability to climb stairs, wheelchair

- Associated with
  - papilledema
  - elevated protein level in cerebrospinal fluid without hypercytosis

- Electromyography (EMG): most often axonal degeneration & demyelination

POEMS: Monoclonal plasma cell proliferation

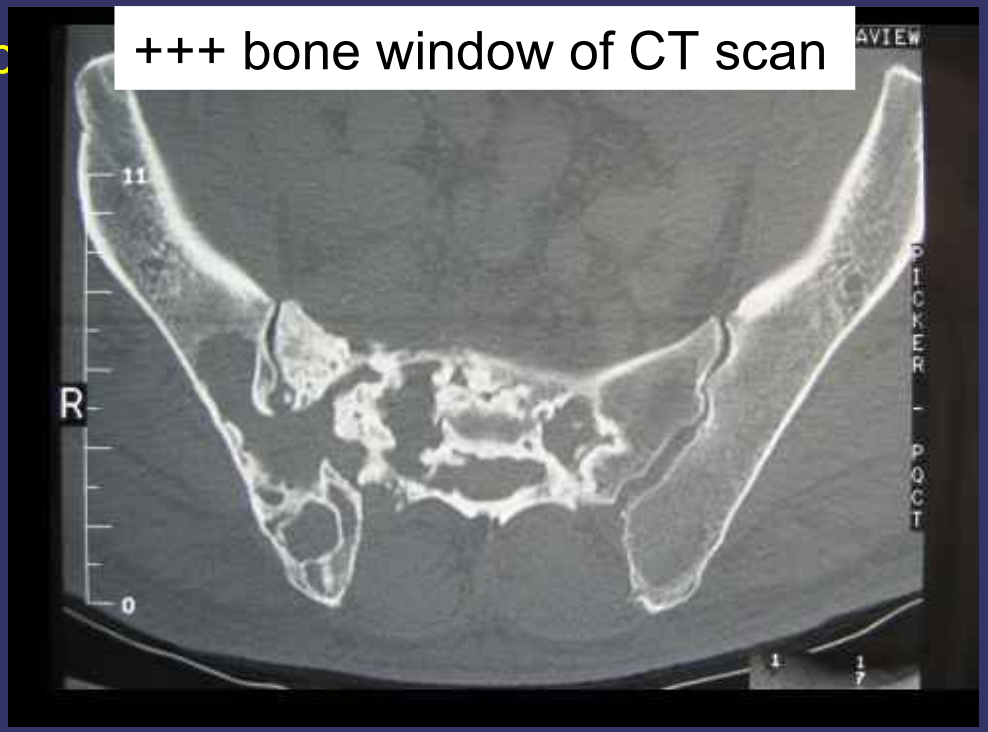
- Asymptomatic
- Bone lesions (54-97%)

  sclerotic (40-98%), diffuse or mixed

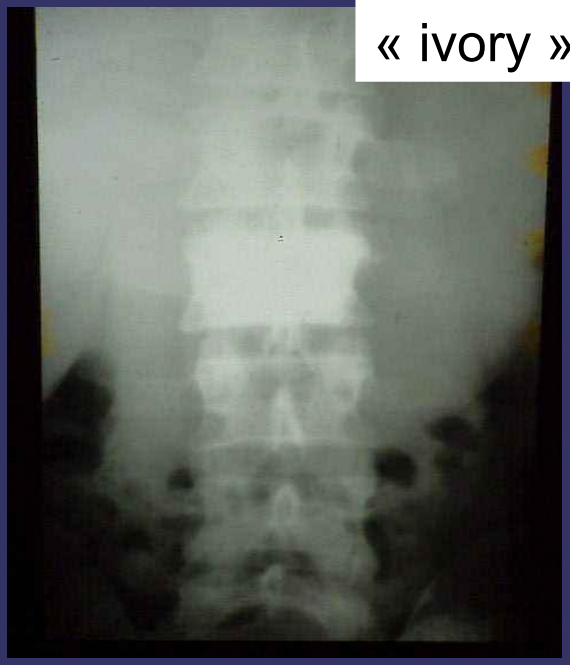
  unique (50%) or multiple

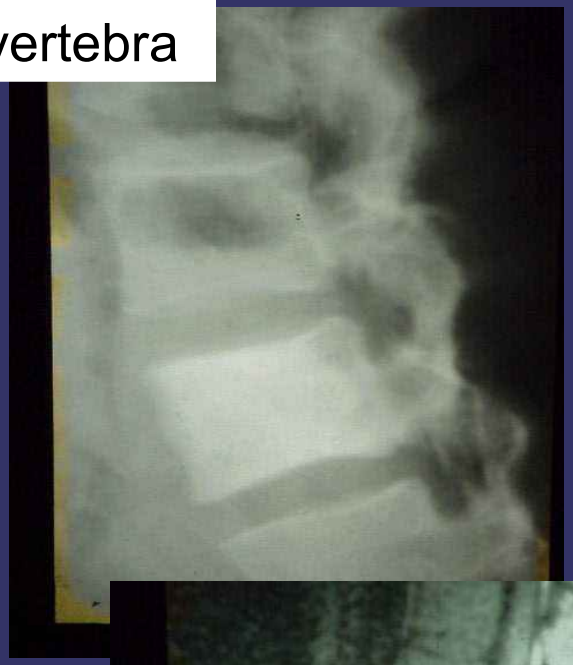
  pelvis +++, rachis and/or rib

Multiple osteosclerotic lesions of the pelvis

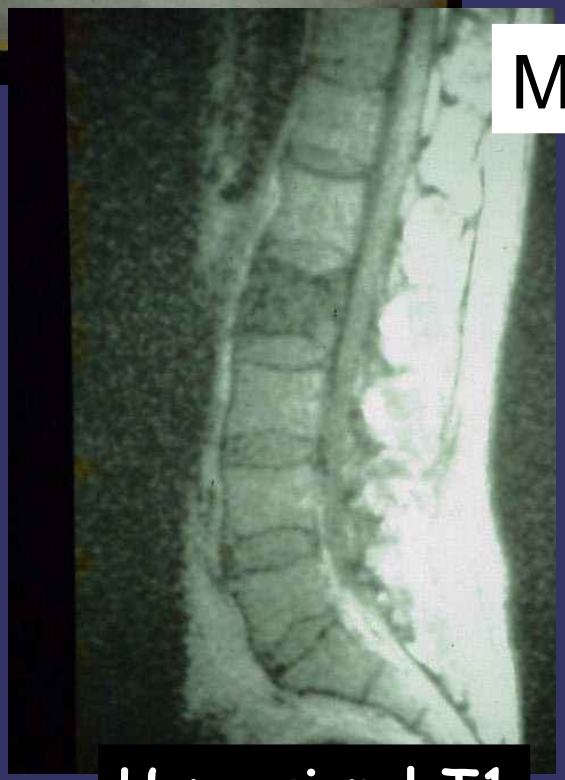


« ivory » vertebra

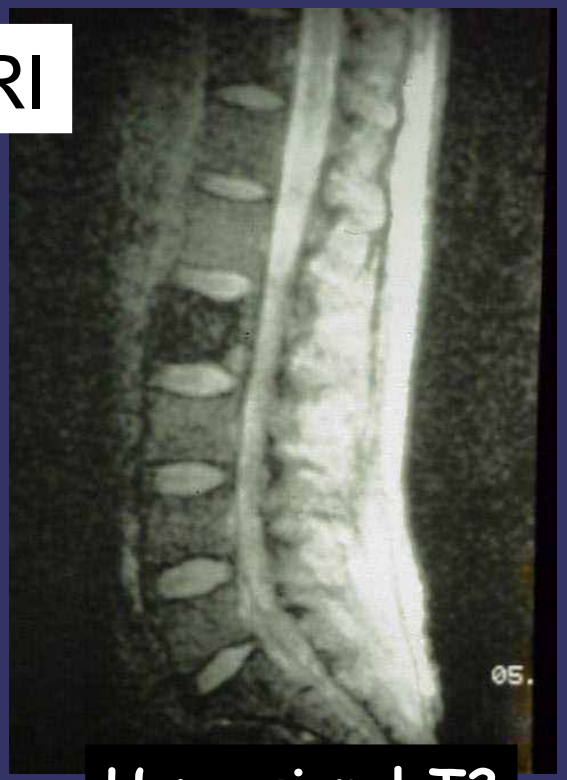




MRI

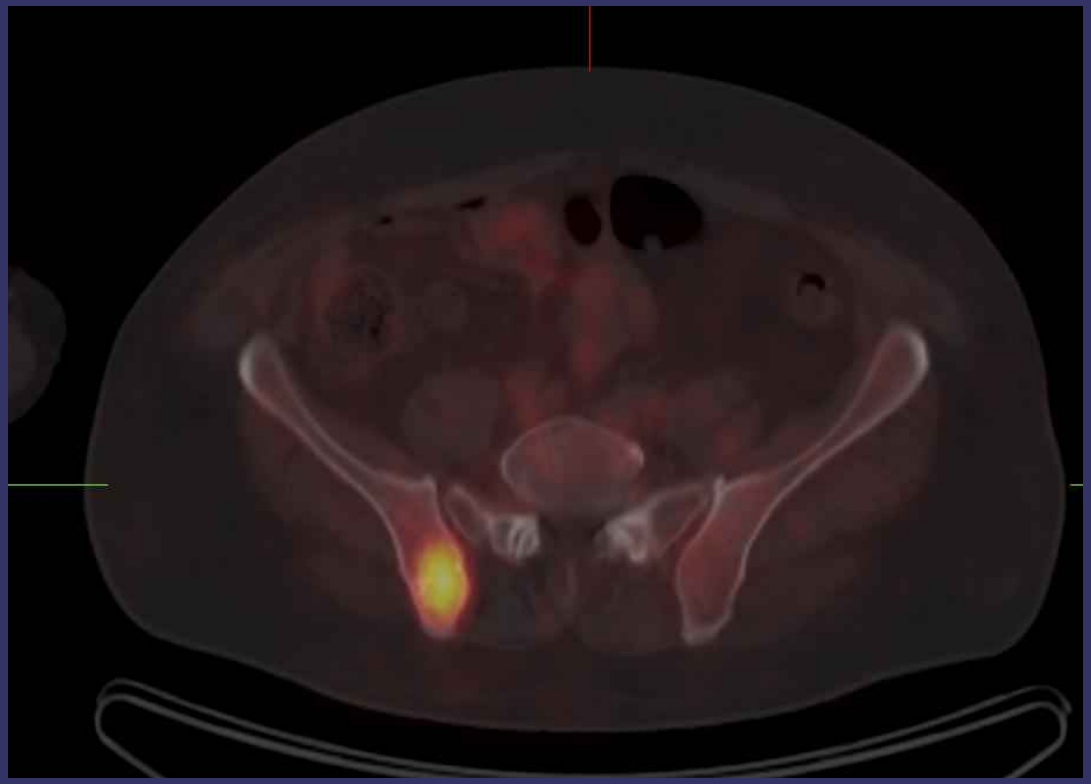


Hypo-signal T1



Hypo-signal T2

PET scan
(variable FDG-avidity)



POEMS: Monoclonal plasma cell proliferation

- Asymptomatic
- Bone lesions (54-9

  sclerotic (40-98%

  unique (50%) or

  pelvis, rachis and/or rib

monoclonal Ig : 75-100%

IgA (45%), IgG (35%),

sometimes IgM or light chain (LC) only

median serum level # 10g/L

usually normal polyclonal Ig level

LC : (almost) always λ

- Usually < 5% plasma cells (PC) in bone marrow

  rarely, PC or lympho-PC infiltration and no bone lesion

POEMS : Organomegaly

- hepatomegaly (24-78%)
  normal hepatic tests or cholestasis
- splenomegaly (22-52%)
- lymphadenopathy (26-61%)

Histology: angiofollicular hyperplasia (Castleman disease) (60%), Polyclonal plasma cell proliferation

POEMS : Endocrinopathy

frequent (up to 85%), often multiple

- hypogonadism (50-90%),
  impotence, gynecomastia, amenorrhea
- hypothyroidism (3-36%), diabetes (14-36%), adrenal insufficiency

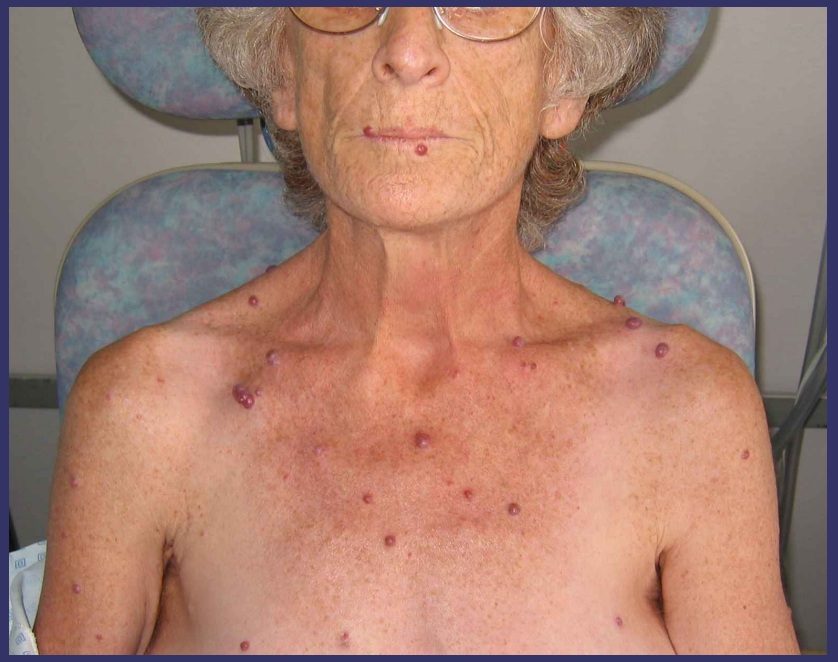
central or peripheral, poorly understood mechanism

POEMS : Skin manifestations

- glomeruloid angiomas

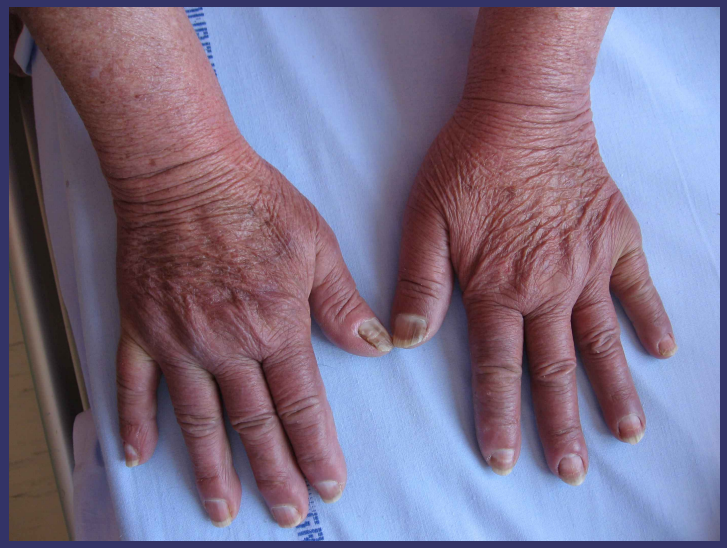
  often rapid accumulation

- hyperpigmentation



- atrophy of the buccal fat pad

- sclerodermiform aspect of extremities
  (skin thickening, acrocyanosis, sclerodactylia)
- clubbing
- hypertrichosis



POEMS : other manifestations

- Systemic symptoms (fever, fatigue, weight loss)
- Edema of extremities

  ascites and pleural effusion
- Vascular manifestations
  - pulmonary hypertension (up to 25%?)
  - arterial and/or venous thromboses
  - vascular glomerulopathy (rare)
- Haematological abnormalities

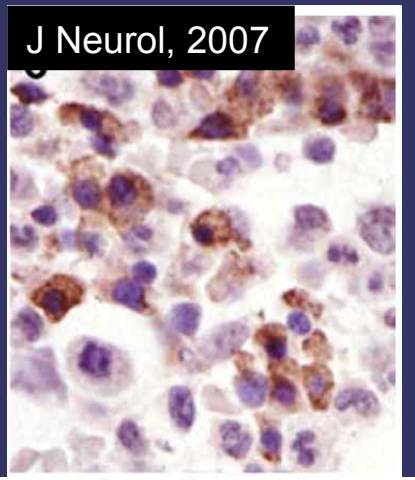
  Thrombocytosis (60 à 90 %), polycythemia (10 à 15 %)

POEMS: physiopathology

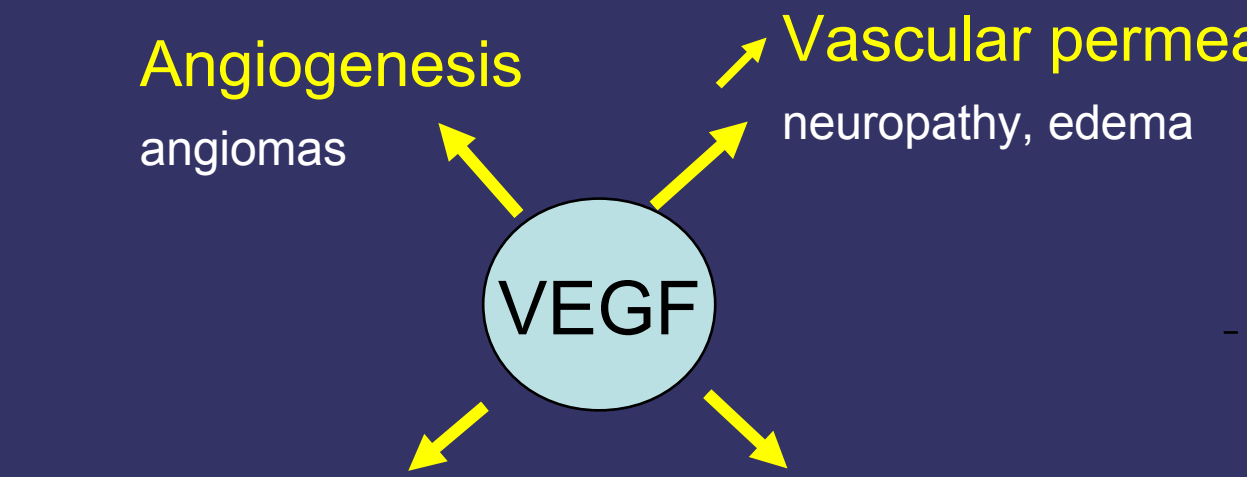
a vascular endothelium growth factor (VEGF) syndrome?

- No known auto-antibody activity
- No monoclonal Ig deposition
- +++ serum VEGF elevation in the majority of patients

major criteria for the diagnosis (Mayo clinic)



Expression of vascular endothelial growth factor by plasma cells in the sclerotic bone lesion of a patient with POEMS syndrome



POEMS: a VEGF syndrome?

Yes, but still some issues

- why almost always λ isotype ?

nucleotide sequencing of IGL gene (n=13 Soubrier et al, Abe et al):

- Vλ1 subfamily, very limited number of germlines, similar CDR3
- hypermutation suggesting antigen-driven selection

relationship with VEGF?
auto-antibody activity enhancing its production?

- why Castelman's disease?

role of HHV8 virus (+ in 100% HIV and 40% non HIV Castelman's disease)?

Common origin from a specific lymphoïd population preferentially using λ chains and secreting VEGF in response to various stimuli (HHV8 …)?

POEMS: treatment

Single or multiple osteosclerotic lesion in a limited area

local radiotherapy (at least 40 gray)

Widespread bone lesions or diffuse BM plasmocytosis

Plasmapheresis/ intravenous immunoglobulin

no neurotoxic drug !

anti-VEGF (bevacizumab)

but high risk of pulmonary leakage)

+++ early diagnosis to prevent irreversible neurological disability

systemic therapy

high dose melphalan
+ autotransplantation

Standard dose chemotherapy (alkylating agents, dexamethasone, lenalidomide)

Effective therapy → response of the various manifestations

slow for neurologic symptoms, rapid for others

even in the absence of a complete hematological response

correlated with VEGF level

Cutaneous, renal and neurological manifestations of plasma cell dyscrasias: conclusions

In patients with monoclonal gammopathy,

clinical examination (including skin and tendon reflexes) and urine protein analysis

may be very fruitful!

Thank you for your attention