Monoclonal Gammopathy of Clinical Significance (MGCS)

Where are we now?

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Monoclonal Gammopathy of Renal/Clinical Significance (MGRS/MGCS)

An achievement of the International Kidney and Monoclonal Gammopathy Group (IKMG)

which introduced the concept

* *Monoclonal gammopathy of renal significance: when MGUS is no longer undetermined or significant, Leung N, Bridoux F, et al.* ***Blood 2012***
* *Monoclonal gammopathy of clinical significance: a novel concept with therapeutic implications, Fermand JP, Bridoux F, et al.* ***Blood 2018***

and made recommendations based on expert opinion

* *How I treat monoclonal gammopathy of renal significance (MGRS)? Fermand JP, Bridoux F, et al.* ***Blood 2013***
* *Diagnosis of monoclonal gammopathy of renal significance. Bridoux F, Leung N, et al.* ***Kidney Int. 2015***
* *The evaluation of monoclonal gammopathy of renal significance: a consensus report of the IKMG. Leung N, et al.* ***Nat Rev Nephrol. 2019***

Monoclonal Gammopathy of Renal/Clinical Significance (MGRS/MGCS)

A successful but trendy concept?

PubMed research for MGRS, n=395

Occasional confusions and misunderstanding ….

MGRS/MGCS:

Resolving definition issues

MGRS/MGCS: resolving definition issues

MGC(R)S:
a small « dangerous » secreting B-cell clone + related symptoms

= a monoclonal gammopathy

+

no overt associated lympho and/or plasma cell proliferation

+

associated symptoms related to the monoclonal immunoglobulin (MIg) or to the B-cell clone by any mechanism other than the tumor burden

MGRS/MGCS: resolving definition issues

Offscreen

* **Monoclonal gammopathy with tumor-mass related symptoms**
(including cast nephropathy),
to be treated per se
= *symptomatic Myeloma (MM), Waldenström macroglobulinemia (WM) …*

* **Symptomatic MM, WM + non tumor-mass related complications**
= *MM with AL, WM with cryoglobulinemia ….*

In the field

MGUS
or **indolent** MM, WM .... + related symptoms

= MGCS with AL, with LCDD ...
or MGCS-related AL, MGCS-related LCDD…

MGRS/MGCS: resolving definition issues

MGCS or MGRS?
according to targeted organs:

MGCS with renal involvement only

PGNMID
(Proliferative GN with MIg deposits)

GOMMID
(Immunotactoid nephropathy)

C3 glomerulopathy

Fanconi syndrome /LCPT

MGCS with renal and systemic involvement

AL(H) amyloidosis

Monoclonal Ig deposition disease (LCDD and others)

Type I and II cryoglobulinemia

Thrombotic microangiopathy

Cristal-storing histiocytosis

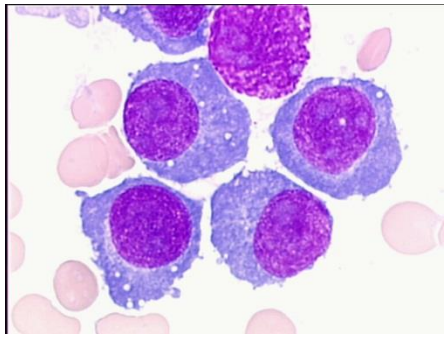
MGCS usually without renal involvement

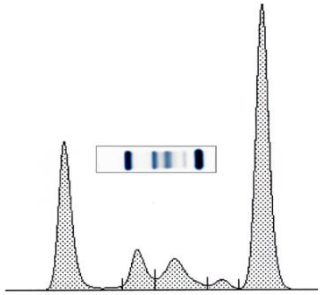
Monoclonal gammopathy of cutaneous, neurological or other significance?

MGRS/MGCS:

Pathophysiology: still many uncertainties

MGC(R)S: Pathophysiology: still many uncertainties





Cytokine

Deposition

Auto-antibody activity of MIg

all or part of MIg

aggregates: fibrillar, crystalline, microtubular

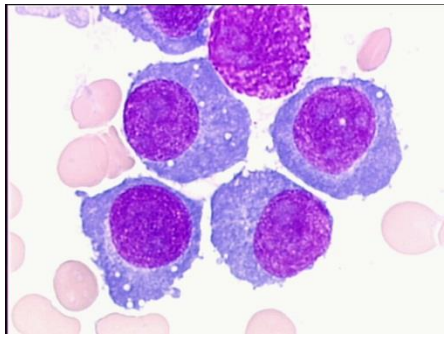
Immune complexes

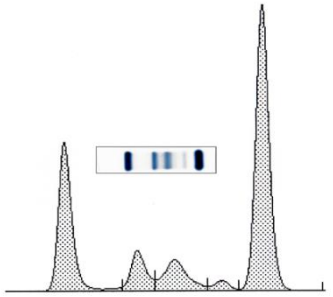
against a tissue antigen

Intra-vascular (±vasculitis)

Intra-cellular ex: xanthoma

MGC(R)S: Pathophysiology: still many uncertainties





Cytoki

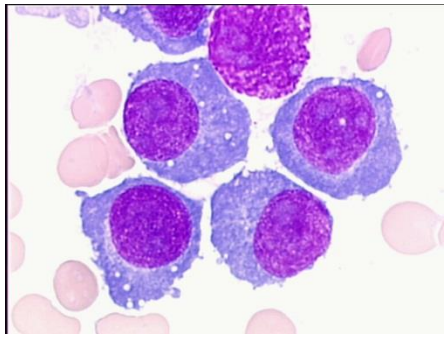
Deposition

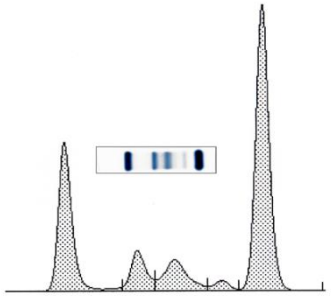
Auto-antibody activity of MIg

New mechanism:
interaction MIg-complement alternative pathway
(C3 glomerulopathy, thrombotic microangiopathy)

against biologically active molecules

MGC(R)S: Pathophysiology: still many uncertainties





Cytokine

Deposition

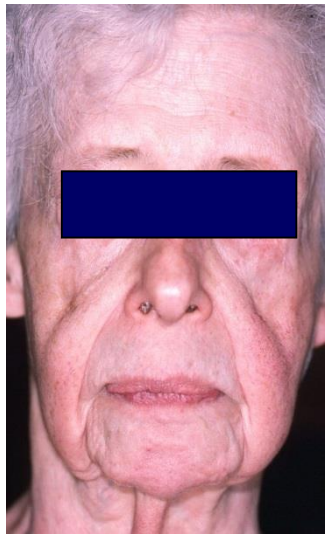
Auto-antibody activity of MIg

Other mechanism?

Schnitzler, scleromyxoedema, cutis laxa, pyoderma

TEMPI, Capillary leak syndrome

MGC(R)S: Pathophysiology: still many uncertainties



Acquired cutis laxa (ACL)

Rare disorder of elastic tissue
resulting in loose, redundant, hypoelastic skin
and, sometimes, systemic manifestations (lung, GI tract)

Various reported associations, including IgG or IgA monoclonal gammopathy
sometimes with γ heavy chain deposition disease (HCDD)

In a recent series* (n=14, including 4 with HCDD)

- γ heavy chain deposition on residual elastic fibers in all patients with HCDD
- Negative IF studies in other cases except one with positive ar

Elastic tissue destruction by complement activation and release of elastases in patients with ACL and HCDD?
In other cases?

*Jachiet et al. J Am Acad Dermatol, 201

MGC(R)S:

Diagnostic challenges

MGC(R)S: Diagnostic challenges

Early detection is key

Careful clinical work-up in baseline evaluation and follow-up of all monoclonal gammopathies,
looking at any renal and extra-renal manifestation, including:

- search and characterization of proteinuria
- Serum cardiac biomarkers?

Systematic serum protein electrophoresis (sPEP) and urine PEP
in general medical practice

Serum and urine immunofixation (IF) studies if any doubt,
systematic in patients with suggestive renal, cutaneous or neurological manifestations
systematic in pts with renal symptoms without an obvious cause?

MGC(R)S: Diagnostic challenges

In a patient with monoclonal gammopathy
+ renal and/or extra-renal symptoms

- Characterization of monoclonal gammopathy
  - Nature of the clone (plasmacytic *or* lymphoplasmocytic (IgM)
  - Symptomatic or indolent MM, WM, or other B-cell lymphoma, or MGUS

    Rare but not to be missed: solitary plasmocytoma or other localized B-cell proliferation

- Diagnosis of renal and/or extra-renal disease

  tissue (renal) biopsy usually required

MGC(R)S: Diagnostic challenges

If no evidence for monoclonal gammopathy

= detecting the pathogenic clone

e.g. in a patient with renal monotypic Ig deposits (or C3 only)

- Repetition of serum and urine immunochemical studies (including sFLC)
- +++ Confirmation that Ig deposits are m[illegible]otypic
  - if IgG: subclass typing
  - in selected cases, proteomic or othe[illegible]
- **If still no detectable serum/urine [illegible]**
  FLC excess)
  - Complete blood and/or bone m[illegible]
  cytometry and molecular bi[illegible]gy
  - CT or PET-scan

If deposits **actually** monotypic even if no detected clone by any techniques

there is (was) one!

MGC(R)S: Diagnostic challenges

Monoclonal gammopathy + renal and/or extra-renal symptoms: causal relationship?

Crucial to exclude a chance association

High prevalence of MIg, particularly in the elderly

I/4 patients with senile amyloidosis (usually elderly males) have an MIg …

MGC(R)S: Diagnostic challenges

Excluding a chance association

✧ Most often = demonstration of MIg deposition in affected organ

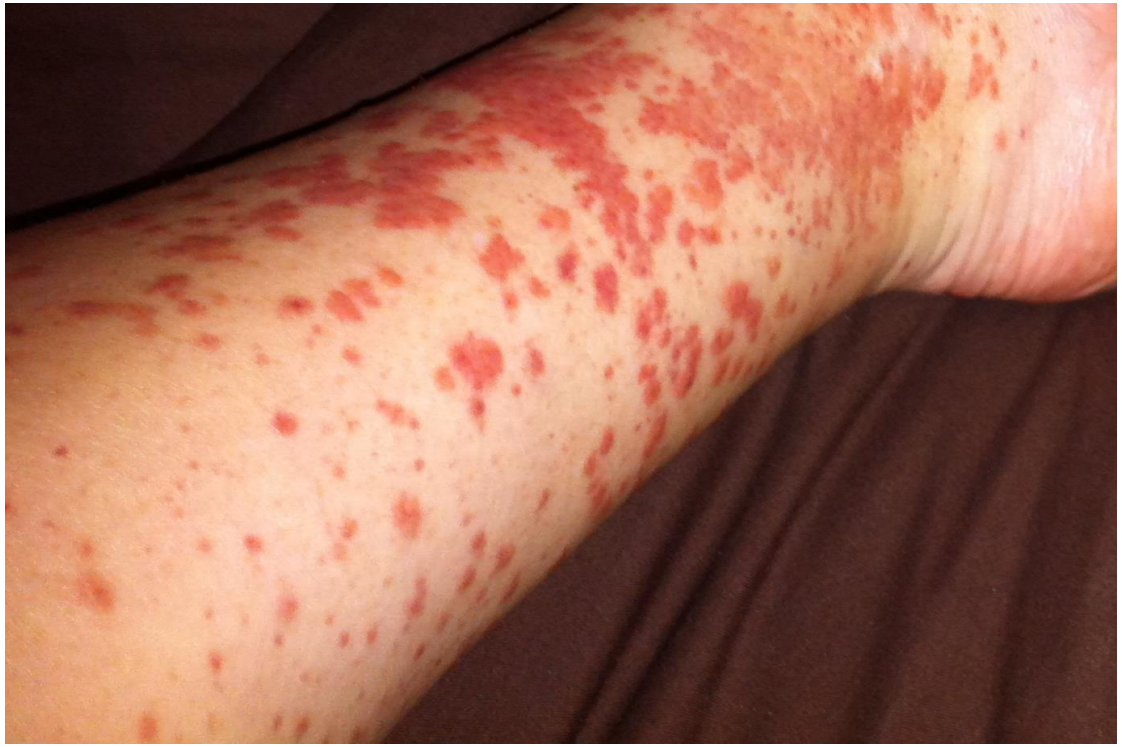
Immuno-histological techniques (using antibodies specific for LC isotypes and, when appropriate, anti-IgG subclasses)

Ig deposits with LC restriction, matching the circulating MIg

In selected cases, (immuno)electron microscopy and proteomic studies

MGC(R)S: Diagnostic challenges

Vascular purpura lesions due to type II mixed cryoglobulinemia



Histological lesions*: vasculitis with apparently polytypic Ig deposits*

(made of the monoclonal rheumatoid IgM + polyclonal IgG)

MGC(R)S: Diagnostic challenges

Excluding a chance association

✧ Most often = demonstration of MIg deposition in affected organ

Immuno-histological techniques (using antibodies specific for LC isotypes and, when appropriate, anti-IgG subclasses)

Ig deposits with LC restriction, matching the circulating MIg

In selected cases, (immuno)electron microscopy and proteomic studies

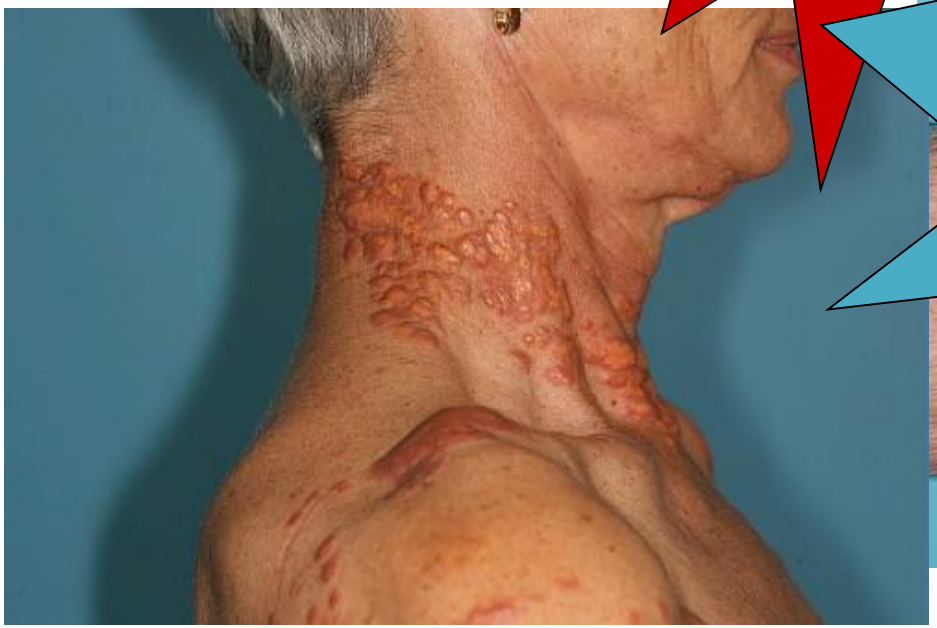
✧ For MIg-mediated immune process

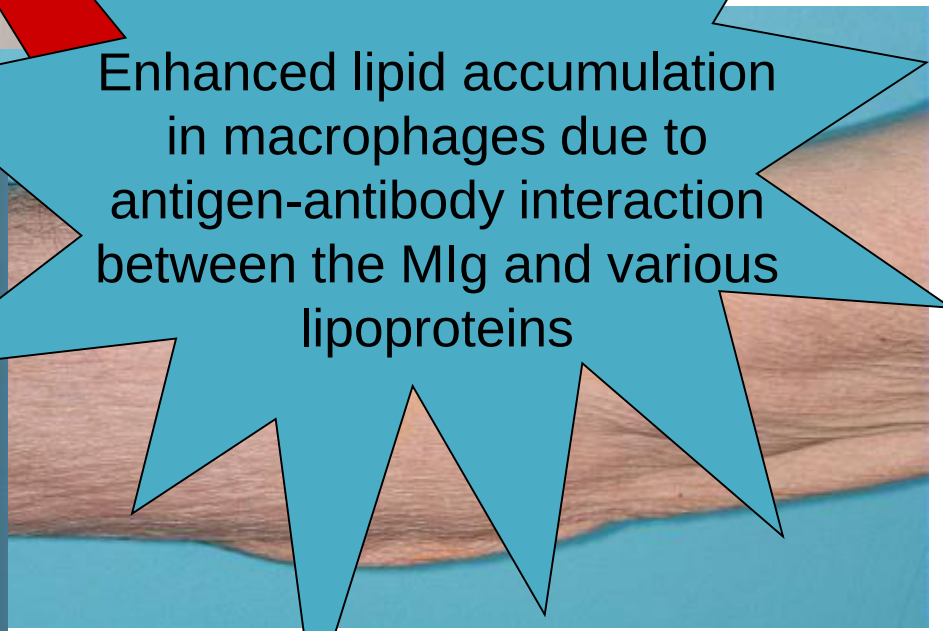
High titer of auto-antibody activity

Hypocomplementemia

Xanthomas
(+ normal serum lipids)
and MIg

Low serum
complement (C4 …) levels
++-





Enhanced lipid accumulation
in macrophages due to
antigen-antibody interaction
between the MIg and various
lipoproteins

(Szalat et al. Blood, 2011)

MGC(R)S: Diagnostic challenges

Excluding a chance association

✧ For MIg-mediated immune process

To be distinguished:

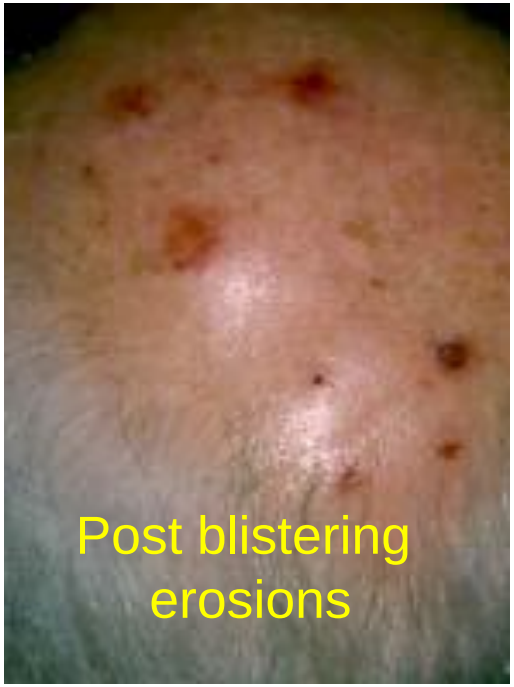
- **Monoclonal auto-antibody activity**

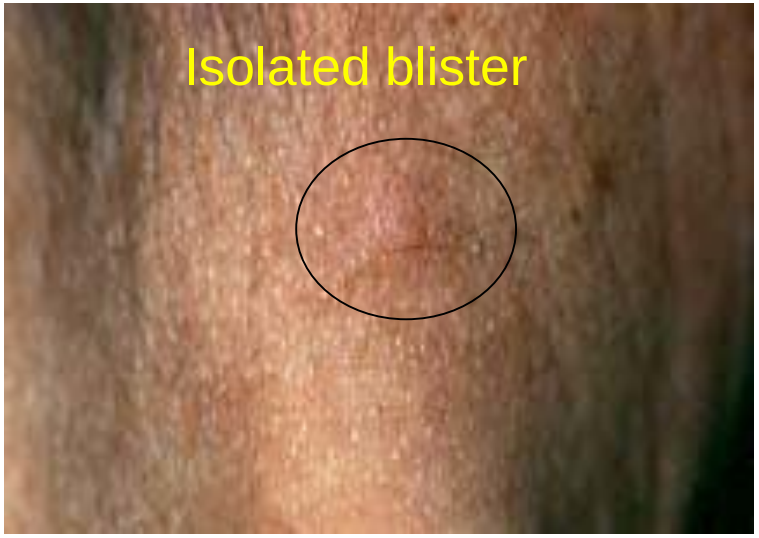
  e.g. monoclonal IgM anti-IgG Fc (type II cryoglobulinemia)
  anti-red blood cells (cold agglutinin disease)
  anti-myelin associated glycoprotein (anti-MAG neuropathy)

- **Polyclonal auto-antibody activities**

  produced by non clonal bystander B-cells
  sometimes pathogenic (as in auto-immune hemolytic anemia & thrombopenic purpura)
  frequent in CLL, WM and other lymphoid proliferations

Auto-immune bullous skin disease and monoclonal gammopathy





Immuno-histological studies:

linear Ig deposits at dermo-epidermal junction

- ***with LC restriction*** *(likely due to the MIg)*
- ***most often polytypic*** *(likely due to polyclonal auto-antibodies produced by bystander B-cells)*

Immuno-blot:

Usually anti-collagen VII antibody

Aractingi & Fermand, 1999, Medicine

MGC(R)S: Diagnostic challenges

Excluding a chance association

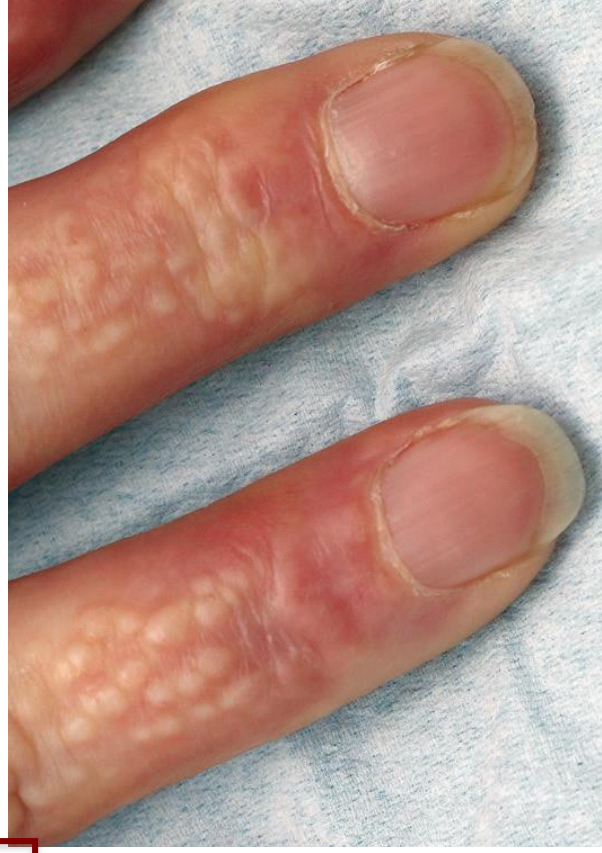
- ✧ Most often = demonstration of MIg deposition in affected organ
- ✧ For MIg-mediated immune process
- ✧ Otherwise
  - epidemiological data

    frequency of the association

    may be used as a diagnostic criterium

Scleromyxedema

Laura K. Hummers



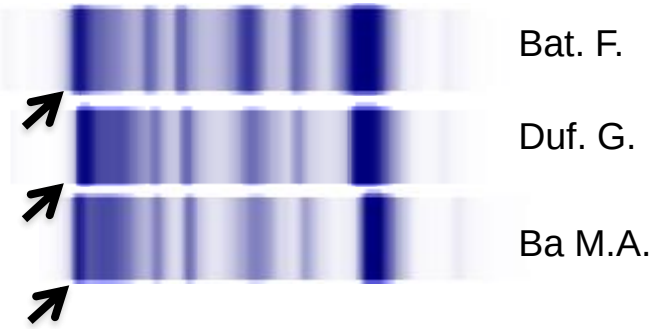
DIAGNOSIS

all four of the following criteria:

(1) papular cutaneous eruption (in a characteristic scleroderma-like distribution);
(2) skin biopsy that demonstrates the cardinal features of scleromyxedema including dermal mucin deposition, proliferation of spindle-like fibroblasts and increase in collagen;
(3) the presence of a monoclonal gammopathy in peripheral blood;
(4) absence of thyroid dysfunction.

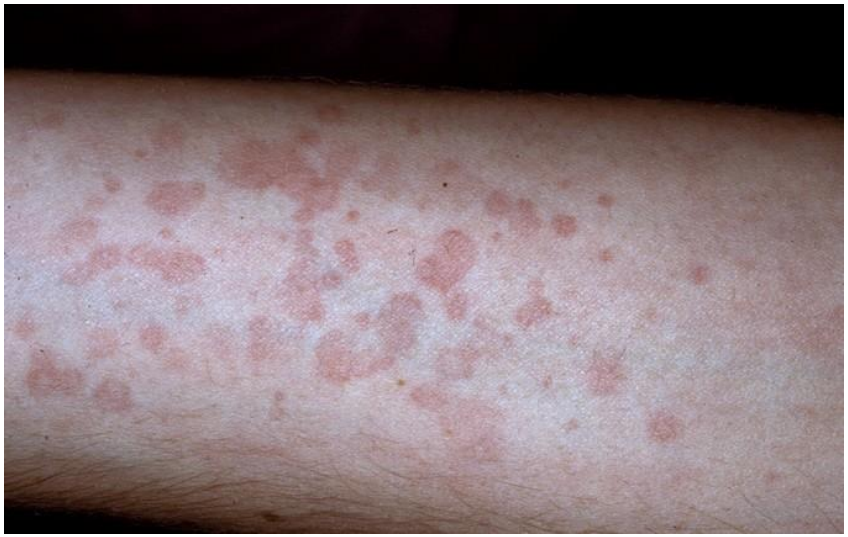
MIg in scleromyxoedema:

usually IgG λ of **slow electrophoretic mobility**



MGC(R)S: Diagnostic challenges

Schnitzler syndrome



Diagnostic criteria

Obligate

Chronic urticarial rash and

Monoclonal IgM or IgG

If IgM, definitive diagnosis when 2 obligate + 1 minor criteria

Minor

Recurrent fever

Objective findings of abnormal bone remodeling

a neutrophilic infiltrate on skin biopsy

Leucocytosis and/or elevated CRP

A. Simon et al, Gusdorf et al. Allergy, 2013 & 2017

MGC(R)S: Diagnostic challenges

Monoclonal gammopathy + renal and/or extra-renal symptoms: **Excluding a chance association**

- Most often = demonstration of MIg deposition in affected organ
- For MIg-mediated immune process
- Otherwise
  - epidemiologic data
  - disease evolution

    response to therapy targeting the clone

    recurrence of associated symptoms with relapse of the gammopathy

MGC(R)S: Diagnostic cha

POEMS syndrome

(monoclonal gammopathy almost always λ

cell proliferation usually focal and causing

+

polyneuropathy, organomegaly, endocrinopathy (th

manifestations)

POEMS =
a VEGF syndrome?

why almost always λ isotype
(with very restricted Vλ gene usage)?

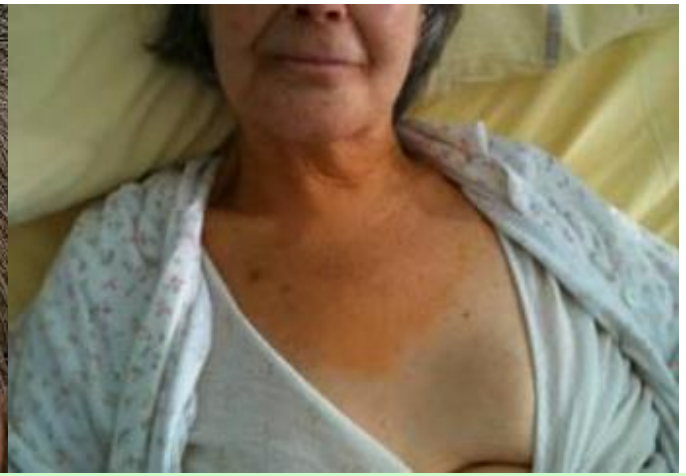
mechanism of enhanced VEGF production

Effective therapy targeting the clone (e.g. irradiation of a solitary plasmocytoma)
= rapid resolution of associated manifestations (slow for neuropathy)
If clonal relapse (new plasmocytoma …)
= recurrence

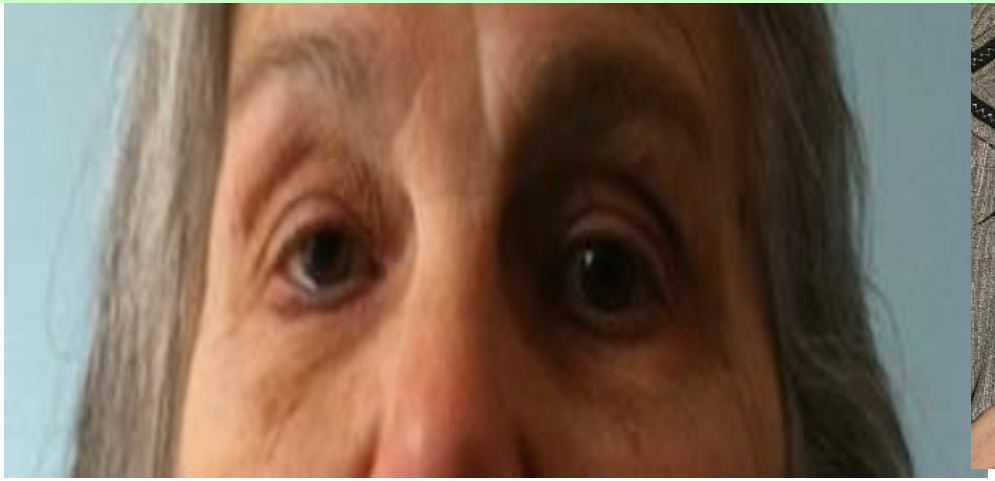
Marked elevation of serum vascular endothelial growth factor (VEGF) level which better correlates with disease activity than MIg level variation

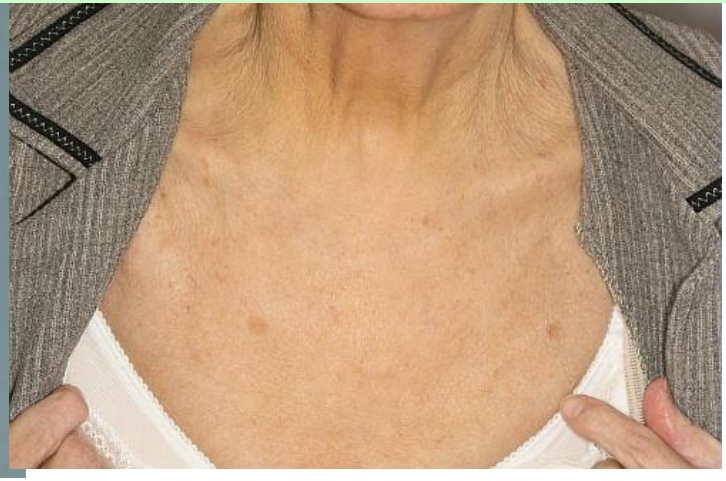
Parallel evolution of clonal proliferation and lipid deposits in MGCS-related Xanthoma

At diagnosis



After achievement of hematological complete remission on bortezomib-based regimen





MGC(R)S: Diagnostic challenges

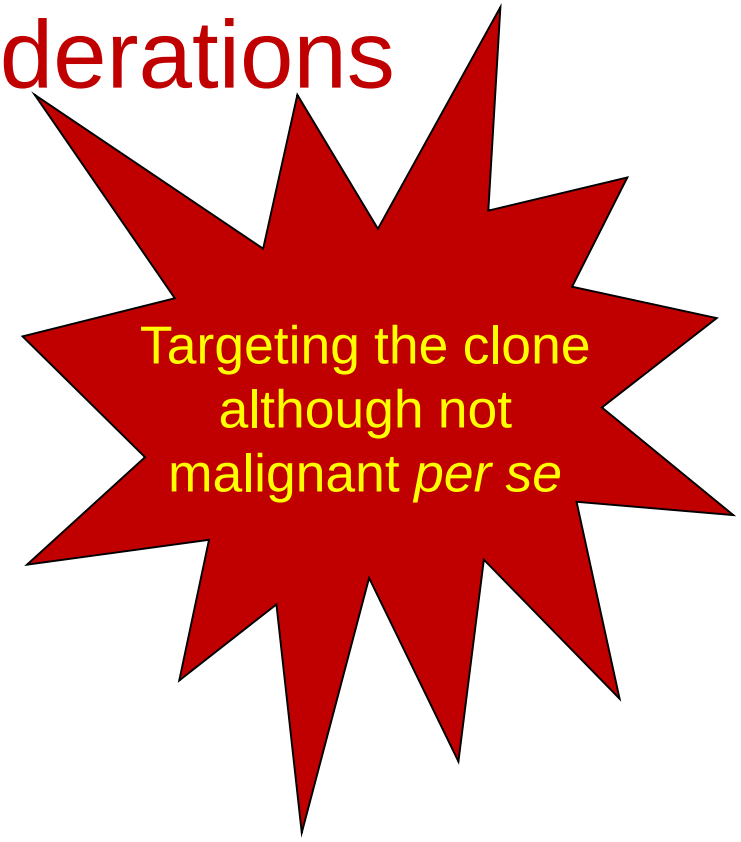
Excluding a chance association

No treatment targeting the B-cell clone in the absence of clear link

If only putative relationship, collegial discussion mandatory (reference center)

MGC(R)S:

Therapeutic considerations



MGC(R)S: Therapeutic considerations

Treatment of renal/extra-renal manifestations = treatment of the clone

The main option = anti B-cell/plasma cell agents, i.e. chemotherapy, monoclonal antibodies and, in selected cases, irradiation

taking into account renal metabolism of drugs

adapted to the nature of the clone

- If plasmacytic : anti-myeloma agents
  - bortezomib-based
  - *anti-CD38 mAb?*
- If lymphocytic or lymphoplasmacytic : treatment similar to MW or CLL
  - anti-CD20-based
  - *Place of non conventional agents (BTK inhibitors) ?*

MGC(R)S: Therapeutic considerations

Selecting therapy based on the underlying clone: the example of cryos

type I cryo (monoclonal)

Cold-induced intravascular MIg precipitation

Usually high amount (1-30g/l)

Negative rhumatoïd factor

Inconstant hypocomplementemia

Monoclonal IgG (#60%), usually CD20-neg. plasmacytic clone

Monoclonal IgM (#40%), lympho-plasmacytic CD20+ clone

Rituximab for IgM cryo

Usually MM therapy for IgG cryo

type II cryo (mixte)

Immune complexe-mediated vasculitis

Low amount (≤ 1 g/l)

Positive rhumatoïd factor

Constant hypocomplementemia

Monoclonal IgM with rheumatoid antibody activity
lympho-plasmacytic CD20+ clone

Treatment of hepatitis C, if associated

Rituximab-based WM therapy if symptomatic (non viral) cryo

MGC(R)S: Therapeutic considerations

As demonstrated by AL and MIDD, for most MGCS:

Quality of hematological response conditions organ response and patient survival

- **Goal of treatment**

achievement of the best hematological response

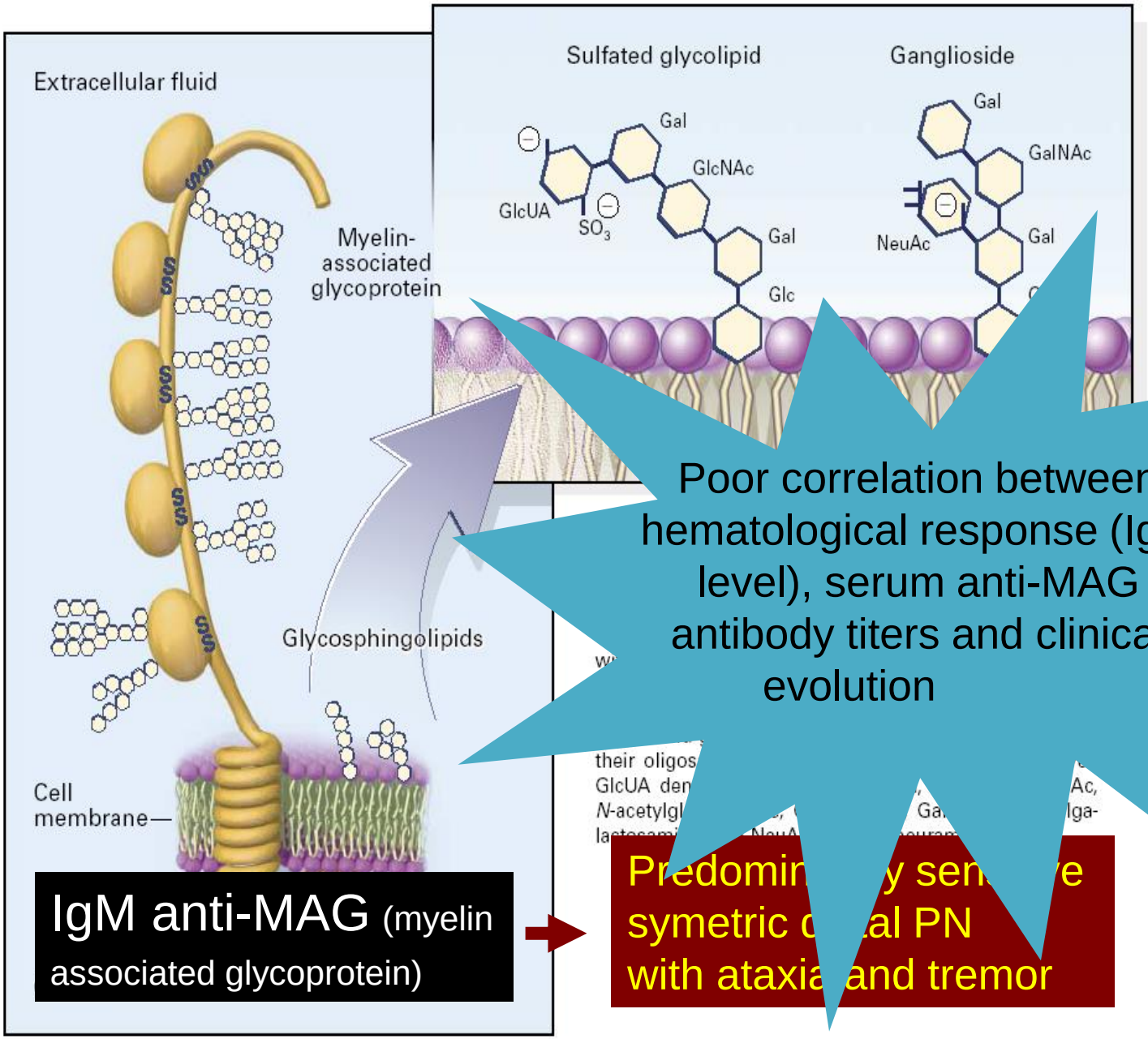
- **Response evaluation**

assessment of hematological response based on serial measurements of pathogenic MIg (usually serum FLC)
Determines treatment adaptation

Organ response not only influenced by hematological response

The hematological response = necessary but not sufficient

Anti-MAG monoclonal IgM and peripheral neuropathy (PN)



Poor correlation between hematological response (IgM level), serum anti-MAG antibody titers and clinical evolution

IgM anti-MAG (myelin associated glycoprotein)

Predomin y sen e symetric al PN with ataxia and tremor

MGC(R)S: Therapeutic considerations

Indication for therapy:

driven by organ damage due to the secreting clone

benefit to risk approach**,** considering:

- involved organs
- natural disease history
- comorbidities

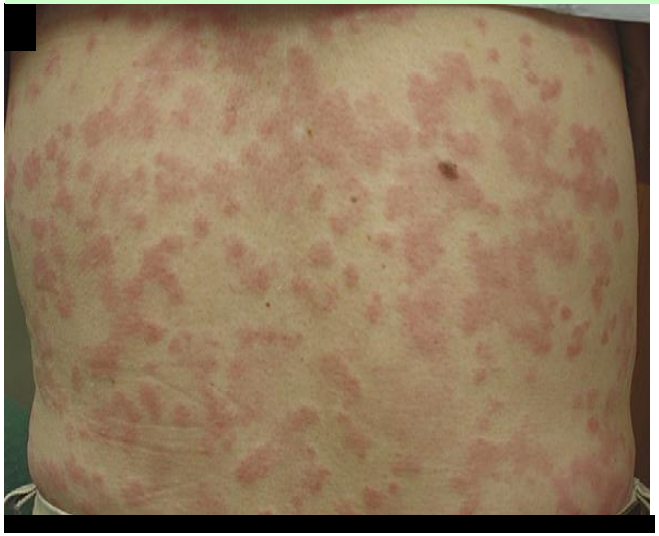
Polychemotherapy and even high dose therapy with autologous blood stem cell transplantation

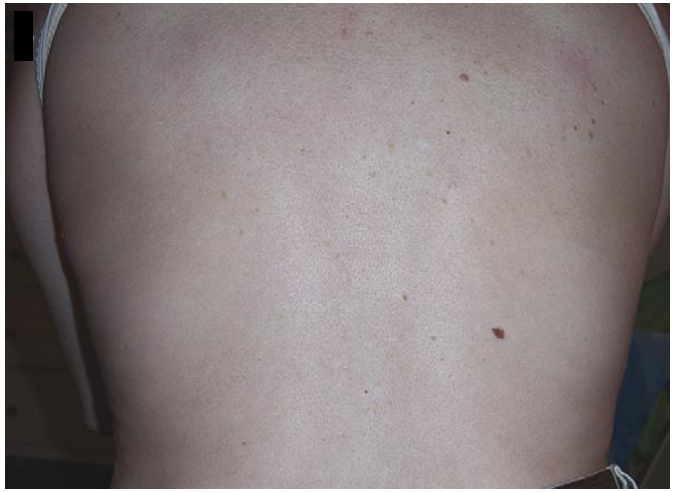
- not questionable in a patient with MGCS and AL
- not appropriate in a patient with MGCS and a slowly progressive skin disorder

MGC(R)S: Therapeut

Particular case: T
Efficacy of

(Anakinra (Ki





Dra
urticaria, fever

Normalization of all er biolog
abnormalities (C-rea ve protein, Hb,
leukocyte and platele counts)

No effect on MIg level

Tapering/cessation of steroids

Sustained but symptomatic efficacy
well tolerated

Schnitzler syndrome =
acquired auto-inflammatory
syndrome?

*Deregulation of IL-1 by
interaction of a clonal product
with the IL1 pathway?*

MGC(R)S: Therapeutic considerations

High-dose intravenous immunoglobulins:

alternative to chemotherapy in some MGCS?

- May be effective in:
  - Anti-ganglioside IgM-associated polyneuropathy (but not in anti-MAG)
  - Scleromyxoedema
  - Systemic capillary leak syndrome
- Efficacy usually temporary
- Long-term use limited by availability, cost and side effects (including renal toxicity)
- Potential mechanisms of action involving inhibition of antibody activity, complement deviation and cellular responses

Monoclonal Gammopathy of Renal/Clinical Significance (MGRS/MGCS)

Conclusions

Thanks to the IKMG research group,
MGC(R)S is now a well established concept

However, additional work required to:

- Spread the knowledge of the concept while [illegible] ambiguities regarding its outlines
- Better understand the pathophysiology of the vari[illegible] related conditions
- Favor early diagnosis
- Improve management and treatment

Thanks to **Frank Bridoux** for his help and contributions

Thank you for your attention