Monoclonal Gammopathy of Clinical Significance (MGCS)

Where are we now?

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


and made recommendations based on expert opinion

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:

<table>
<thead>
<tr>
<th>MGCS with renal involvement only</th>
<th>MGCS with renal and systemic involvement</th>
<th>MGCS usually without renal involvement</th>
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<tbody>
<tr>
<td>PGNMID (Proliferative GN with Mlg deposits)</td>
<td>AL(H) amyloidosis</td>
<td>Monoclonal gammopathy of cutaneous, neurological or other significance?</td>
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<tr>
<td>GOMMID (Immunotactoid nephropathy)</td>
<td>Monoclonal Ig deposition disease (LCDD and others)</td>
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<tr>
<td>C3 glomerulopathy</td>
<td>Type I and II cryoglobulinemia</td>
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<tr>
<td>Fanconi syndrome /LCPT</td>
<td>Thrombotic microangiopathy</td>
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<td>Cristal-storing histiocytosis</td>
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MGRS/MGCS:
Pathophysiology: still many uncertainties
MGC(R)S: Pathophysiology: still many uncertainties

- **Cytokine**
  - all or part of MIg

- **Deposition**
  - aggregates: fibrillar, crystalline, microtubular

- **Auto-antibody activity of MIg**
  - Immune complexes
  - against a tissue antigen
  - Intra-vascular (± vasculitis)
  - Intra-cellular ex: xanthoma

- MGC(R)S: Pathophysiology:
MGC(R)S: Pathophysiology: still many uncertainties

New mechanism: interaction Mlg-complement alternative pathway (C3 glomerulopathy, thrombotic microangiopathy)
MGC(R)S: Pathophysiology: still many uncertainties

Cytokine → Deposition → Other mechanism? → Schnitzler, scleromyxoedema, cutis laxa, pyoderma → TEMPI, Capillary leak syndrome → Auto-antibody activity of Mlg
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 anti-λ LC staining.

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, 2018
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?
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 monotypic
  • if IgG: subclass typing
  • in selected cases, proteomic or other?

➢ If still no detectable serum/urine Ig or FLC excess
  - Complete blood and/or bone marrow cytometry and molecular biology
  - CT or PET-scan

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

there is (was) one!
High prevalence of MIg, particularly in the elderly

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

Crucial to exclude a chance association

Monoclonal gammopathy + renal and/or extra-renal symptoms: causal relationship?
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
Vascular purpura lesions due to type II mixed cryoglobulinemia

Histological lesions: \textit{vasculitis with apparently polytypic Ig deposits}
\((\text{made of the monoclonal rheumatoid IgM} + \text{polyclonal IgG})\)
Excluding a chance association

Most often = demonstration of Mlg 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 Mlg*

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

For Mlg-mediated immune process

High titer of auto-antibody activity

Hypocomplementemia
Xanthomas (+ normal serum lipids) and Mlg

Low serum complement (C4 ...) levels

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

(Szalat et al. Blood, 2011)
MGC(R)S: Diagnostic challenges

Excluding a chance association

✧ For M Ig-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 M*lg*)
  - *most often polytypic* (likely due to polyclonal auto-antibodies produced by bystander B-cells)

Immuno-blot:
*Usually anti-collagen VII antibody*
MGC(R)S: Diagnostic challenges

Excluding a chance association

✧ Most often = demonstration of Mlg deposition in affected organ

✧ For Mlg-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.

Mlg in scleromyxoedema:

usually IgG \( \lambda \) of *slow electrophoretic mobility*

Bat. F.
Duf. G.
Ba M.A.
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 challenges

POEMS syndrome
(monoclonal gammopathy almost always \(\lambda\) isotype
with very restricted \(V\lambda\) gene usage)
+ polyneuropathy, organomegaly, endocrinopathy, skin (and other)
manifestations)

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

Targeting the clone although not malignant *per se*
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

<table>
<thead>
<tr>
<th>type I cryo (monoclonal)</th>
<th>type II cryo (mixte)</th>
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<tbody>
<tr>
<td>Cold-induced intravascular MiG precipitation</td>
<td>Immune complexe-mediated vasculitis</td>
</tr>
<tr>
<td>Usually high amount (1-30g/l)</td>
<td>Low amount (≤ 1 g/l)</td>
</tr>
<tr>
<td>Negative rhumatoïd factor</td>
<td>Positive rhumatoïd factor</td>
</tr>
<tr>
<td>Inconstant hypocomplementememia</td>
<td>Constant hypocomplementememia</td>
</tr>
</tbody>
</table>

- **Monoclonal IgG (#60%), usually CD20-neg. plasmacytic clone**
- **Monoclonal IgM (#40%), lympho-plasmacytic CD20+ clone**

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<th>Treatment of hepatitis C, if associated</th>
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<tr>
<td><strong>Rituximab for IgM cryo</strong></td>
</tr>
<tr>
<td><strong>Usually MM therapy for IgG cryo</strong></td>
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</table>
**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)

Predominantly sensitive symmetric distal PN with ataxia and tremor.

Poor correlation between hematological response (IgM level), serum anti-MAG antibody titers and clinical evolution.
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
Particular case: The Schnitzler syndrome

Efficacy of IL-1 receptor antagonist (Anakinra (Kineret*) 100 mg/day SC)

- 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 IgM level

Tapering/cessation of steroids

Sustained but symptomatic efficacy well tolerated
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
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 removing ambiguities regarding its outlines
- Better understand the pathophysiology of the various related conditions
- Favor early diagnosis
- Improve management and treatment

Thanks to Frank Bridoux for his help and contributions.

Thank you for your attention.