



Disponible en ligne sur

**ASJP**  
Algerian Scientific Journal Platform

<https://www.asjp.cerist.dz/en/PresentationRevue/588>



## ARTICLE ORIGINAL

# Clinicobiological and immunological characteristics of monoclonal gammopathies associated with autoimmune diseases: a retrospective single-center analysis of 162 cases

Profil clinicobiologique et immunologique des gammopathies monoclonales associées aux maladies auto-immunes: étude rétrospective monocentrique sur 162 cas

Melissa BELALA <sup>a,b,\*</sup>, Fatma MERAH <sup>a</sup>, Reda DJIDJIK <sup>a,c</sup>

<sup>a</sup> Laboratoire d'immunologie médicale, CHU Béni-Messous

<sup>b</sup> Faculté de médecine, Université des sciences de la santé

<sup>c</sup> Faculté de pharmacie, Université des sciences de la santé

## MOTS CLÉS

Gammopathies monoclonales (MGUS, myélome multiple) ;  
Maladies auto-immunes (MAI);  
Polyarthrite rhumatoïde (PR) ;  
Lupus érythémateux systémique;  
Profil immunologique ;  
Caractéristiques cliniques ;  
Scores pronostiques (Mayo Clinic, ISS-R).

## Résumé

**Introduction :** Les gammopathies monoclonales sont fréquentes chez le sujet âgé, toutefois leur association aux maladies auto-immunes (MAI) reste mal caractérisée. Cette étude vise à décrire les caractéristiques cliniques, immunologiques et pronostiques des patients présentant une gammopathie monoclonale associée à une MAI, et à les comparer à la population générale des gammopathies suivie dans notre service.

**Méthodes :** Étude rétrospective monocentrique incluant 162 patients ayant à la fois une gammopathie monoclonale (MGUS ou myélome multiple – MM) et une MAI, entre 2015 et 2025. Les données ont été comparées aux 5020 cas de gammopathies recensés sur la même période dans notre service. Les caractéristiques démographiques, les types de MAI, les isotypes, la concentration du composant monoclonal (CM) et les scores pronostiques (Mayo Clinic, ISS-R) ont été analysés.

**Résultats :** La MGUS représentait 73.45 % des cas. L'âge moyen au diagnostic était de 54,75 ans, inférieur à celui des gammopathies isolées (63–65 ans). Une prédominance féminine marquée (69,75 %) a été observée. Les MAI les plus fréquentes étaient la polyarthrite rhumatoïde (30,86 %), le syndrome de Gougerot-Sjögren (11,11 %) et le lupus érythémateux systémique (7,4 %). L'isotype IgG Kappa était majoritaire (37,65 %), avec une concentration moyenne de CM modérée (4,12 g/L). Les scores pronostiques classaient la majorité des MGUS en faible risque évolutif. Des pics monoclonaux transitoires ou fluctuants étaient plus fréquents que dans les gammopathies isolées.

**Conclusion :** Les gammopathies monoclonales associées aux MAI présentent un profil épidémiologique et immunologique distinct, avec un diagnostic plus précoce, une prédominance féminine et des taux globalement modérés de CM. Bien que les données pronostiques soient

**KEYWORDS**

Monoclonal  
gammopathy (MGUS,  
multiple myeloma);  
Autoimmune diseases  
(AID);  
Rheumatoid arthritis;  
Sjögren's syndrome;  
Systemic lupus  
erythematosus;  
Immunological profile;  
Clinical features;  
Prognostic scores  
(Mayo Clinic, ISS-R).

rassurantes, le contexte auto-immun impose un suivi prolongé, en raison d'un risque évolutif potentiellement modulé mais encore mal défini.

© 2025 Revue Algérienne d'Allergologie et d'Immunologie Clinique. Tous droits réservés.

**Abstract**

**Introduction:** Monoclonal gammopathies are common in elderly individuals, but their association with autoimmune diseases (AID) remains poorly characterized. This study aims to describe the clinical, immunological, and prognostic features of patients with monoclonal gammopathy associated with an AID, and to compare them with the general population of gammopathies followed in our department.

**Methods:** This is a single-center retrospective study including 162 patients with both monoclonal gammopathy (MGUS or multiple myeloma – MM) and an AID, between 2015 and 2025. Data were compared with 5,020 cases of gammopathies recorded during the same period in our department. Demographic characteristics, types of AID, isotypes, monoclonal component (MC) concentration, and prognostic scores (Mayo Clinic, ISS-R) were analyzed.

**Results:** MGUS accounted for 73.45% of cases. The mean age at diagnosis was 54.75 years, lower than that of isolated gammopathies (63–65 years). A marked female predominance (69.75%) was observed. The most frequent AIDs were rheumatoid arthritis (30.86%), Sjögren's syndrome (11.11%), and systemic lupus erythematosus (7.4%). The predominant isotype was IgG Kappa (37.65%), with a moderate mean MC concentration (4.12 g/L). Prognostic scores classified most MGUS cases as low risk of progression. Transient or fluctuating monoclonal spikes were more frequent than in isolated gammopathies.

**Conclusion:** Monoclonal gammopathies associated with AID show a distinct epidemiological and immunological profile, with earlier diagnosis, female predominance, and overall moderate MC levels. Although prognostic data are reassuring, the autoimmune context requires long-term follow-up, due to a potentially modulated but still poorly defined risk of progression.

© 2025 Revue Algérienne d'Allergologie et d'Immunologie Clinique. All rights reserved.

\* Auteur correspondant :

Adresse e-mail : belamelissa@gmail.com (M. BELALA)

**Introduction:**

A monoclonal immunoglobulin is the secretory product of a single clone of B lymphocytes or plasma cells, secondary to a clonal proliferation. This immunoglobulin may be complete, consisting of two heavy chains and two associated light chains, or incomplete, containing only light chains (kappa or lambda), or more rarely, only heavy chains. Monoclonal gammopathies (MG) are clonal proliferations of plasma cells or lymphoplasmacytic cells, responsible for the secretion of a monoclonal protein or paraprotein. An MG may reveal a malignant hematologic disease (multiple myeloma – MM, Waldenström's disease, lymphoma, etc.) or a benign condition, since monoclonality is not synonymous with malignancy

(monoclonal gammopathy of undetermined significance, MGUS). (1)

Multiple myeloma (MM) is a malignant hematologic disorder characterized by the clonal proliferation of plasma cells, leading to bone marrow infiltration and secretion of a monoclonal immunoglobulin in most cases. According to the International Myeloma Working Group (IMWG), MM is defined by the presence of clonal bone marrow plasma cells  $\geq 10\%$  (or a histologically proven osseous or extraosseous plasmacytoma) and at least one of the following criteria:

- **CRAB criteria** (end-organ damage attributable to plasma cell proliferation):
  - Hypercalcemia: serum calcium  $>0.25$  mmol/L ( $>1$  mg/dL) above the upper limit of normal, or  $>2.75$  mmol/L ( $>11$  mg/dL).

- Renal insufficiency: creatinine clearance <40 mL/min or serum creatinine >177 µmol/L (>2 mg/dL).
- Anemia: hemoglobin <10 g/dL or >2 g/dL below the lower limit of normal.
- Bone lesions: at least one osteolytic lesion detected by skeletal X-ray, CT, or PET-CT.
- **Additional criteria introduced in 2014:**
  - Bone marrow plasmacytosis ≥60%.
  - Serum free light chain ratio ≥100 (measured with the Binding Site assay, with the involved light chain ≥100 mg/L).
  - 1 focal lesion ≥5 mm on MRI. (2)

Prognosis is based on the revised International Staging System (R-ISS), the gold standard for newly diagnosed MM, which incorporates serum β2-microglobulin (Sβ2M), serum albumin, cytogenetic abnormalities by iFISH, and LDH levels:

- **Stage I:** Sβ2M <3.5 mg/L, serum albumin ≥3.5 g/dL, standard-risk cytogenetics by iFISH, and normal LDH.
- **Stage II:** Not fitting criteria for stage I or III.
- **Stage III:** Sβ2M ≥5.5 mg/L plus either high-risk cytogenetics by FISH or elevated LDH. (3)

**MGUS is defined by:**

- Absence of CRAB criteria or amyloidosis signs.
- Plasma cell proliferation ≥10% and <60%.
- And/or serum monoclonal protein (IgG or IgA) ≥30 g/L.
- And/or Bence Jones proteinuria ≥500 mg/24 h. (1)

Each year, about 1% of patients with MGUS progress to malignant hematologic disorders such as MM, light-chain amyloidosis, Waldenström macroglobulinemia, or lymphoma. This progression risk depends on several parameters (Mayo Clinic model criteria):

- Type of monoclonal immunoglobulin: IgA or IgM MGUS carries a higher risk of progression than IgG MGUS.
- Serum monoclonal protein concentration: levels >15 g/L are associated with higher progression risk.
- Free light chain ratio (FLC ratio): an abnormal ratio (either too high or too low) indicates higher progression risk.

Combining these factors allows risk stratification:

- **Low risk:** No risk factors or only one low-intensity factor.
- **Intermediate risk:** Two risk factors.
- **High risk:** All three risk factors. (4)

Autoimmune diseases (AID) frequently occur with monoclonal gammopathies, particularly MGUS. AIDs are characterized by increased immune reactivity against autoantigens, causing tissue damage. Although their etiology remains largely unknown, genetic, microbial, environmental, and psychological factors are known contributors. Clinical presentations vary, including organ-

nonspecific autoimmune diseases (e.g., rheumatoid arthritis – RA, Sjögren's syndrome, systemic lupus erythematosus – SLE), and organ-specific diseases (e.g., pernicious anemia). (5)

From a pathophysiological perspective, monoclonal gammopathies result from the clonal emergence of abnormal plasma cells, promoted by several immunological and genetic mechanisms. In the setting of AID, chronic antigenic stimulation and prolonged B-cell activation play central roles. These repeated stimulations promote the expansion of potentially monoclonal plasma cell clones within a proinflammatory environment.

Cytokines such as IL-6, IL-13, and TNF-α are involved in plasma cell proliferation by inhibiting apoptosis, promoting survival, and maintaining chronic activation. This inflammatory state increases the risk of accumulating genetic alterations and malignant transformation into disorders such as MM. (6, 7)

Myeloma plasma cells differ from normal plasma cells by overexpression of Toll-like receptors (TLRs), especially TLR7, TLR9, and TLR4. This abnormal expression alters responses to physiological immune signals, contributing to prolonged survival and abnormal proliferation of tumor cells. Moreover, overexpression of the IL-6 receptor favors autocrine stimulation, enhancing expansion and resistance to pro-apoptotic signals. (8)

At the genomic level, even at early stages such as MGUS, cytogenetic abnormalities are frequently detected. The most common include translocations involving region 14q32 (IgH heavy chain gene), trisomies of odd chromosomes (hyperdiploidy), and deletions of 17p (TP53). (9)

Hyperdiploidy, present in most MGUS cases, is generally associated with a favorable prognosis, except for certain abnormalities such as trisomy 21, which correlates with higher progression risk. In contrast, deletion of chromosome 17p13 is recognized as the most unfavorable prognostic factor, predictive of progression to high-risk MM. (10)

Thus, the occurrence of monoclonal gammopathies in the context of AID lies at the intersection of persistent immuno-inflammatory abnormalities and early cytogenetic disturbances, justifying strict longitudinal monitoring even in the absence of clinical signs of progression.

Progression from MGUS to MM is characterized by bone lesions, osteoclast activation, and osteoblast inhibition. Osteoclast activation is triggered by increased RANKL expression by osteoblasts and possibly plasma cells, along with inhibition of osteoprotegerin (OPG) by CD138. Release of macrophage inflammatory proteins MIP-1α and MIP-1β, as well as expression of stromal cell-derived factor 1α, also contribute to osteoclast activation and bone resorption. (11)

The frequency of monoclonal gammopathies increases with age, affecting 3% of individuals over 50 years and 5% after age 70 (7). The overall prevalence of a monoclonal component (MC) among patients with autoimmune diseases is estimated at around 2%. However, some diseases show much higher rates. For example, Sjögren's syndrome is associated with an MC in 43.9% of cases, with a risk of progression to lymphoma. In SLE, MC is found in 14.6% of patients, a frequency correlated with lymphoproliferative disorders. Finally, a prevalence of 19.5% is observed in patients with rheumatoid arthritis (RA). (6)

### Study objective:

The aim of our work is to analyze the frequency of autoimmune diseases associated with monoclonal gammopathies (MM and MGUS) and to assess their prognostic impact within our cohort. We also aim to describe the clinicobiological and immunological profiles of these patients.

### Materials and methods:

Statistical analysis was performed using Excel 2016 and SPSS software. For quantitative variables, the mean, median, and standard deviation were calculated. For qualitative variables, frequencies were determined. Comparisons were carried out using the Mann-Whitney test for non-parametric variables and the  $\chi^2$  test for categorical data.

A retrospective study was conducted in the Immunology Department of the University Hospital Center of Beni Messous over a 10-year period (2015–2025), including 162 patients.

The mean age of the study population was  $54.75 \pm 16.8$  years. Most patients were women (113/162, 69.75%), while men accounted for 30.24% (49/162), with a sex ratio (M/F) of 0.43.

MM was present in 43 out of 162 patients (26.54%, group 1), including 27 women (62.79%) and 16 men (37.20%), with a sex ratio (M/F) of 0.59. The mean age was  $53.51 \pm 16.95$  years.

MGUS was found in 119 cases (73.45%, group 2), including 86 women (72.26%) and 33 men (27.73%), with a sex ratio (M/F) of 0.38. The mean age was  $55.26 \pm 16.8$  years.

These patients underwent the following serum and urinary immunological tests:

- **Serum Protein Electrophoresis (SPEP):**

SPEP is an essential laboratory method for the qualitative and quantitative analysis of major serum protein fractions. It highlights a monoclonal component in the gamma, beta, or, more rarely, alpha region. It appears as a narrow, dense, and symmetrical band in one of these zones. The test was performed using either capillary techniques

(Capillarys Octa 3® – Sebia, V8® – Helena) or agarose gel electrophoresis (SAS3®, SAS4® – Helena, Hydrasys Focusing® – Sebia).

- **Serum Protein Immunofixation (IFE):**

IFE confirms the presence of a monoclonal component and identifies precisely the immunoglobulin isotype (IgG, IgA, IgM, etc.) and the type of light chain (kappa or lambda). It was performed using SAS3®, SAS4® Helena Biosciences, or Hydrasys Focusing Scan® Sebia.

- **Serum Beta-2-Microglobulin Assay:**

This assay was performed by laser nephelometry using BNproSpec®, and carried out in only 11 patients from group 1.

- **Serum Free Light Chains (sFLC) Assay and FLC Ratio Calculation:**

Performed by turbidimetry on SPA Plus® or laser nephelometry on BNproSpec®, or on SPA Plus Binding Site. It was done in 5 patients from group 1 and 6 patients from group 2.

- **Urine Protein Electrophoresis (UPEP):**

Conducted on agarose gel (SAS3®, SAS4® Helena®, or Hydrasys Focusing Scan®, Sebia®), performed in 8 patients from group 1 and 3 patients from group 2.

- **Urine Protein Immunofixation:**

Performed using SAS3 IFE-9 kits (SAS3®, SAS4®, Helena®) or Bonce Jonce kits (Hydrasys Focusing Scan®).

Some of our patients also underwent an **autoimmunity workup**, including the detection of antinuclear antibodies (ANA) by indirect immunofluorescence (IIF) on HEp-2 cells or by chemiluminescence (CLIA) (MAGLUMI X3). Identification of specific autoantibodies was performed using Immunodot (dot-blot), ELISA (enzyme-linked immunosorbent assay), or CLIA. All techniques were carried out in our immunology laboratory in accordance with manufacturer recommendations, with both internal and external quality control.

## Results:

### 1. Clinical Data:

**Group 1 (MM):** Characterized by CRAB features, notably anemia in 34.88% (15/43), renal insufficiency in 20.93% (9/43), and bone lesions in 27.90% (12/43). Clinical manifestations related to autoimmune diseases were also observed: joint involvement (arthritis and arthralgia) in 34.88% (15/43), sicca syndrome (ocular–oral dryness) in 16.27% (7/43), and pleuropulmonary manifestations in 13.95% (6/43). Other manifestations, such as nephrotic syndrome,

proteinuria, hepatic, and cutaneous involvement, were noted at much lower frequencies.

**Group 2 (MGUS):** Clinical manifestations were more frequent, dominated by joint involvement in 49.57% (59/119), followed by sicca syndrome in 21.84% (26/119), pleuropulmonary manifestations in 13.44% (16/119), and cutaneous manifestations in 6.72% (8/119). Other signs, including nephrotic syndrome, proteinuria, hematuria, digestive, and hepatic involvement, were reported but with much lower frequencies.

**Table 1. Demographic and clinical data**

| Parameters                        | Group 1 (MM, n=43) | Group 2 (MGUS, n=119) | Total (n=162)    | Comments                                       |
|-----------------------------------|--------------------|-----------------------|------------------|------------------------------------------------|
| <b>Epidemiological data</b>       |                    |                       |                  |                                                |
| Mean age ± SD                     | 53.51 ± 16.95 yrs  | 55.26 ± 16.8 yrs      | 54.75 ± 16.8 yrs | Younger than literature (65–70 yrs, Kyle 2006) |
| Sex ratio (M/F)                   | 0.59               | 0.38                  | 0.43             | Opposite to classical sex ratio (M/F ≈ 1.7)    |
| <b>Clinical data</b>              |                    |                       |                  |                                                |
| Anemia                            | 15 (34.9%)         | /                     | /                | Typical of MM                                  |
| Renal insufficiency               | 9 (20.9%)          | /                     | /                | Consistent with literature                     |
| Bone lesions                      | 12 (27.9%)         | /                     | –                | Classical in MM                                |
| Joint involvement                 | 15 (34.9%)         | 59 (49.6%)            | 74 (45.7%)       | More frequent in MGUS                          |
| ocular and salivary gland dryness | 7 (16.3%)          | 26 (21.8%)            | 33 (20.4%)       | Consistent with SS (20–44%)                    |
| pleuropulmonary manifestations    | 6 (13.9%)          | 16 (13.4%)            | 22 (13.6%)       | Similar frequencies                            |

|                                                                     |      |             |             |                       |
|---------------------------------------------------------------------|------|-------------|-------------|-----------------------|
| Nephrotic syndrome, proteinuria, hepatic, and cutaneous involvement | Rare | 17 (14.28%) | 24 (14.81%) | More frequent in MGUS |
|---------------------------------------------------------------------|------|-------------|-------------|-----------------------|

## 2. Frequencies of Autoimmune Diseases (AID):

**Group 1 (MM):** The most common AID was rheumatoid arthritis (RA) in 18.60% (8/43), followed by pernicious anemia and Sjögren's syndrome, each in 16.27% (7/43), and celiac disease in 9.30% (4/43). Unclassified autoimmune diseases accounted for 16.27% (7/43). Systemic lupus erythematosus (SLE), ANCA-associated vasculitis, and membranous glomerulonephritis were each found in 4.65% (2/43). Systemic sclerosis and inflammatory bowel disease (IBD) were noted in one patient each (2.32%).

**Group 2 (MGUS):** RA was also the most frequent AID, identified in 35.29% (42/119), followed by unclassified AID in 15.96% (19/119), Sjögren's syndrome in 14.28% (17/119), SLE in 8.40% (10/119), and systemic sclerosis in 5.88% (7/119). Autoimmune liver diseases (autoimmune hepatitis and primary biliary cholangitis) were found in 4.2% (5/119). Autoimmune thyroiditis, polymyositis, and ankylosing spondylitis were found in 2.52% each (3/119). ANCA vasculitis, celiac disease, pernicious anemia, and IBD were each observed in 1.68% (2/119). A single case was reported for antiphospholipid syndrome and autoimmune pancreatitis (0.84% each).

**Overall cohort (n=162):** RA was the most frequent AID, present in 32.09% (52/162), followed by unclassified AID in 21.84% (26/162), Sjögren's syndrome in 14.19% (23/162), SLE in 7.40% (12/162), pernicious anemia in 5.55% (9/162), systemic sclerosis in 4.93% (8/162), and celiac disease in 3.7% (6/162). Autoimmune liver diseases were present in 3.08% (5/162). Less frequent AIDs comprised ANCA vasculitis (2.46%), polymyositis, inflammatory bowel disease, ankylosing spondylitis, and autoimmune thyroiditis (1.85% each), membranous glomerulonephritis (1.23%), and more rarely antiphospholipid syndrome and autoimmune pancreatitis (0.61% each).

**Table 2. Frequency of autoimmune diseases**

| Parameter s                                   | Group 1 (MM, n=43) | Group 2 (MGUS, n=119) | Total (n=162) | Comments |
|-----------------------------------------------|--------------------|-----------------------|---------------|----------|
| <b>Frequency of autoimmune diseases (AID)</b> |                    |                       |               |          |

|                                                |                |                |               |                                          |
|------------------------------------------------|----------------|----------------|---------------|------------------------------------------|
| Rheumatoid arthritis                           | 8<br>(18.6%)   | 42<br>(35.3%)  | 52<br>(32.1%) | Most frequent AID (10–40% in literature) |
| Sjögren's syndrome                             | 7<br>(16.3%)   | 17<br>(14.3%)  | 23<br>(14.2%) | Consistent with literature (20–44%)      |
| Systemic lupus erythematosus (SLE)             | 2<br>(4.6%)    | 10<br>(8.4%)   | 12<br>(7.4%)  | Lower than literature (10–15%)           |
| Pernicious anemia                              | 7<br>(16.3%)   | 2<br>(1.7%)    | 9<br>(5.6%)   | More frequent in MM                      |
| Systemic sclerosis                             | 1<br>(2.3%)    | 7<br>(5.9%)    | 8<br>(4.9%)   | Rare but described                       |
| Celiac disease                                 | 4<br>(9.3%)    | 2<br>(1.7%)    | 6<br>(3.7%)   | More frequent in MM                      |
| Unclassified AID                               | 7<br>(16.3%)   | 19<br>(16.0%)  | 26<br>(16.1%) | Similar proportions                      |
| Rare AID (ANCA vasculitis, MG, IBD, APS, etc.) | Isolated cases | Isolated cases | <5%           | Rare but consistent with literature      |

### 3. Immunological Data:

**Group 1 (MM):** Monoclonal MM (single M-protein) was predominant (79.06%, 34/43), followed by biclonal MM (16.27%, 7/43) and triclonal MM (4.65%, 2/43). The most frequent isotype was IgG Lambda (34.88%, 15/43), followed by IgG Kappa (27.90%, 12/43), IgA Kappa (11.62%, 5/43), and light-chain Kappa (2.32%, 1/43). Other rare combinations included IgA Lambda (2.32%), IgG Lambda + IgM Kappa (6.97%), IgA Lambda + IgG Kappa (2.32%), double IgG Lambda/Kappa (2.32%), IgG + double IgM (2.32%), and IgG + double IgA (2.32%). The mean M-protein concentration was  $4.75 \pm 1.06$  g/L. Electrophoretic migration was mostly in the gamma region (83.72%, 36/43), less often in the beta region (9.30%, 4/43), and in both beta and gamma regions in biclonal/triclonal cases (6.97%, 3/43). Hypogammaglobulinemia was found in 32.55% (14/43). Bence Jones proteinuria (BJP) was tested in 8 patients (18.60%) and was positive. Beta-2 microglobulin was measured in 12 patients (27.90%), with a mean level of  $4.07 \pm 3.67$  g/L. ISS staging (based on available data) classified 58.33% (7/12) in stage I, 8.33% (1/12) in stage II, and 25% (3/12) in stage III. Free light chain assay was

performed in 5 patients (11.62%), with abnormal results in 2 and normal in 3.

**Group 2 (MGUS):** Monoclonal MGUS was predominant (77.31%, 92/119), followed by biclonal MGUS (19.32%, 23/119) and triclonal MGUS (3.36%, 4/119). The most frequent isotype was IgG Kappa (42.85%, 51/119), followed by IgG Lambda (26.89%, 32/119) and IgA Lambda (5.88%, 7/119). Other rare isotypes included IgM Lambda (1.68%) and combinations such as IgG Lambda + IgM Kappa (4.20%), double IgG Lambda (0.84%), IgG + IgA + Lambda light chain (1.68%), etc. The mean M-protein concentration was  $4.13 \pm 4.16$  g/L. Migration was mostly in the gamma region (81.51%, 97/119), less often in the beta region (14.28%, 17/119). Hypogammaglobulinemia was present in 21% (25/119). BJP was tested in 3 patients (2.5%) and was positive. Free light chain assay was performed in 7 patients. Prognostic evaluation (based on isotype and M-protein concentration) showed that 67.7% (77/119) had no risk factors, 35.29% (42/119) had one risk factor (mostly non-IgG isotypes), and 2 patients had abnormal FLC ratio. Overall, most patients had a favorable prognosis.

**Overall cohort (n=162):** Monoclonal gammopathy (single M-protein) was predominant (77.77%, 126/162), followed by biclonal (18.51%, 30/162) and triclonal (3.70%, 6/162). The mean M-protein concentration was  $4.12 \pm 4.34$  g/L. Migration was mostly in the gamma region (82.09%, 133/162), less often in the beta region (12.96%, 21/162). Biclonal and triclonal cases showed beta/gamma and beta/gamma/gamma migration patterns (3.08% and 0.61%, respectively). The most frequent isotype was IgG Kappa (38.88%, 63/162), followed by IgG Lambda (29.01%, 47/162), IgA Kappa (5.55%, 9/162), and IgA Lambda (4.93%, 8/162). Several combinations were also noted: IgG + IgM (4.93%), double IgG (6.17%), IgA + IgG (3.08%), etc. Hypogammaglobulinemia was present in 24.07% (39/162). BJP was positive in 6.79% (11/162).

**Table 3. Immunological data.**

| Parameters                    | Group 1 (MM, n=43)  | Group 2 (MGUS, n=119) | Total (n=162)       | Comments                                |
|-------------------------------|---------------------|-----------------------|---------------------|-----------------------------------------|
| Immunological data            |                     |                       |                     |                                         |
| Mean M-protein conc. $\pm$ SD | $4.75 \pm 1.06$ g/L | $4.13 \pm 4.16$ g/L   | $4.12 \pm 4.34$ g/L | Moderate means, overall concordant with |

|                       |                       |                      |                      |                                                                                         |
|-----------------------|-----------------------|----------------------|----------------------|-----------------------------------------------------------------------------------------|
|                       |                       |                      |                      | literature                                                                              |
| Monoclonal GM         | 34<br>(79.1%)         | 92<br>(77.3%)        | 126<br>(77.8%)       | Monoclonal predominant, consistent with literature                                      |
| Biclonal GM           | 7<br>(16.3%)          | 23<br>(19.3%)        | 30<br>(18.5%)        | Higher than general series (<10%), may reflect chronic antigenic stimulation due to AID |
| Triclonal GM          | 2<br>(4.7%)           | 4<br>(3.4%)          | 6<br>(3.7%)          | Rare                                                                                    |
| Predominant isotype   | IgG Lambda<br>(34.9%) | IgG Kappa<br>(42.9%) | IgG Kappa<br>(38.9%) | Consistent with literature (IgG majority)                                               |
| Predominant isotype   | IgG Lambda<br>(34.9%) | IgG Kappa<br>(42.9%) | IgG Kappa<br>(38.9%) | Consistent with literature (IgG majority)                                               |
| Positive BJP          | 8<br>(18.6%)          | 3<br>(2.5%)          | 11<br>(6.8%)         | Typical of MM                                                                           |
| <b>Migration site</b> |                       |                      |                      |                                                                                         |
| Gamma                 | 36<br>(83.72%)        | 97<br>(81.51%)       | 133<br>(82.09%)      | In line with published series (>80%)                                                    |
| Beta                  | 4<br>(9.30%)          | 17<br>(14.28%)       | 21<br>(12.96%)       | Beta position rarer, often associated with IgA                                          |
| Beta/Gamma            | 1<br>(2.32%)          | 3<br>(2.52%)         | 4<br>(2.46%)         | Rare                                                                                    |
| Beta/Gamma/Gamma      | 2<br>(4.65%)          | 2<br>(1.68%)         | 4<br>(2.46%)         | Rare                                                                                    |

| Prognostic factors |                                   |                                  |   |                                        |
|--------------------|-----------------------------------|----------------------------------|---|----------------------------------------|
| ISS (MM)           | Stage I: 58.3%;<br>Stage III: 25% | /                                | / | Mostly good prognosis but small sample |
| Mayo Clinic (MGUS) | /                                 | 67.7% no risk;<br>35.3% one risk | / | Overall low-risk cohort                |

### Discussion:

Within the immunology department of our university hospital, 5,020 cases of monoclonal gammopathies were recorded between 2015 and 2025. In comparison, our current study cohort represents 3.22% of all cases. Although modest, this proportion brings together patients with a dual characteristic: the presence of a monoclonal gammopathy (MGUS or MM) associated with an autoimmune disease. This subgroup therefore deserves particular attention because of its potentially distinct epidemiological, semiological, and prognostic value.

In our study, MGUS represented the most frequently observed monoclonal gammopathy, affecting 119 out of 162 patients, i.e., 73.45% of the study population. This predominance is consistent with literature data, which identify MGUS as an entity far more frequent than multiple myeloma (MM) or other malignant lymphoid hemopathies (13). The prevalence of MGUS increases with age, affecting around 3% of individuals over 50, and up to 5% after 70 years, according to large epidemiological series such as Kyle et al. (2006), who conducted a large-scale cohort study on more than 21,000 patients from Minnesota (13).

Unlike the classical data described by Kyle et al. (2006), which reported a male predominance in monoclonal gammopathies (male-to-female ratio ~1.7), our study shows a clear female predominance (69.75%). This divergence could be explained by an immunological selection bias, since autoimmune diseases are more frequent in women, suggesting a distinct pathophysiological profile in our cohort (13).

The mean age at diagnosis was  $54.75 \pm 16.8$  years, significantly younger than that observed in the general GM population of our department, estimated at 63–65 years (internal CHU Beni Messous data, 2014–2025). Literature data report that monoclonal gammopathies generally occur at an advanced age, with a median age at diagnosis between 65 and 75 years, depending on the GM

type. MGUS is often detected around 70 years, while multiple myeloma is usually diagnosed between 69 and 71 years (14,15). Several autoimmune diseases, particularly systemic lupus erythematosus (SLE), preferentially affect young adults, with a peak incidence around 30 years. This distribution could explain the earlier age observed in our cohort.

In Group 1, we observed that rheumatoid arthritis (RA) was the most frequent autoimmune disease (23.25%), followed by Biermer's disease (16.27%) and Sjögren's syndrome (SS) (13.95%). Rarer AIDs such as celiac disease or ANCA-associated vasculitis were also present. In Group 2, RA was also the most frequent AID (35.29%), followed by Sjögren's syndrome (14.28%) and systemic lupus erythematosus (8.40%). A variety of rarer pathologies were also observed: systemic sclerosis, autoimmune thyroiditis, autoimmune hepatopathies, etc. Moreover, rheumatoid arthritis (RA) was present in 52 patients (32.09%) of our cohort, with a clear predominance in the MGUS group. The prevalence of monoclonal components (MC) in RA patients is estimated at around 10–19%, according to Kyle et al. (2006) (13). A Swedish study by Baecklund (2021) demonstrated that RA increased the risk of developing lymphoid malignancies, including MGUS and MM, by 2- to 3-fold (17). The retrospective Polish study by Wojciechowska et al. (2020) also found RA to be the most frequent AID in patients with MG, with a frequency of 40%, comparable to that observed in our MGUS group (18).

Sjögren's syndrome (SS) was present in 23 patients (14.19%) of our cohort, the majority in the MGUS group. SS is one of the autoimmune diseases most strongly associated with monoclonal gammopathies. The prevalence of MC in SS patients varies between 20% and 45%, reaching 43.9% in some studies. This strong association is explained by chronic B-cell stimulation, favoring clonal proliferation (19).

Systemic lupus erythematosus (SLE) was present in 12 patients (7.4%) of our cohort. The frequency of detecting monoclonal components in SLE patients has been estimated at around 14–15%. Recent studies (Zucchi et al., 2025) confirm this prevalence and emphasize that the presence of such components increases the risk of progression to lymphoproliferative disorders, including lymphomas and multiple myeloma (20). In our cohort, Biermer's disease was found in 9 (5.55%) patients with monoclonal components, whereas the cited study reported a 13.6% incidence of cobalamin deficiency among patients with IgA myeloma and MGUS. Furthermore, a case-control study showed a 1.47-fold increased risk of

developing myeloma among patients with Biermer's disease, suggesting a potential epidemiological link between these two entities (21).

Other AIDs such as systemic sclerosis, celiac disease, ANCA-associated vasculitis, or Hashimoto's thyroiditis were observed at frequencies ranging from 1% to 5%. These frequencies are broadly in line with the literature, which describes them as less frequently associated with monoclonal gammopathies, yet not negligible. Overall, the frequencies observed in our cohort are somewhat higher than expected. These data support the hypothesis that autoimmune diseases, by promoting prolonged B-cell activation, increase the risk of monoclonal clone emergence, thus providing a favorable ground for the development of MGUS and even MM.

The table below illustrates a comparison of the frequencies of autoimmune diseases associated with monoclonal gammopathies in our cohort and in the literature:

**Table 4. Distribution of autoimmune diseases in patients with monoclonal gammopathies – our single-center study and literature comparison**

| Autoimmune disease                 | Frequency in our cohort (%) | Frequency in literature (%) | References                                            |
|------------------------------------|-----------------------------|-----------------------------|-------------------------------------------------------|
| Rheumatoid arthritis (RA)          | 32.09%                      | 10–20–40%                   | Baecklund 2021; Filik 2016; Wojciechowska et al. 2020 |
| Sjögren's syndrome (SS)            | 14.19%                      | 20–44%                      | Ramos-Casals 2019; Voulgaris 1997                     |
| Systemic lupus erythematosus (SLE) | 7.4%                        | 10–15%                      | Muchtar 2018                                          |
| Biermer's disease                  | 5.55%                       | 2–5%                        | Azzabi 2017                                           |
| Systemic sclerosis                 | 4.93%                       | ~3–5%                       | Various studies                                       |
| Celiac disease                     | 3.7%                        | <3%                         | Limited data                                          |
| ANCA-associated vasculitis         | 2.46%                       | <2%                         | Limited data                                          |

|                                    |               |     |              |
|------------------------------------|---------------|-----|--------------|
| Autoimmune thyroiditis / Hashimoto | 1.85%         | <2% | Limited data |
| IBD / APS / Polymyositis           | 1.23% or less | <2% | Limited data |

### Immunological Findings:

In our cohort, the IgG Kappa isotype was the most frequently observed, affecting 38.88% of patients, followed by IgG Lambda (29.01%), and then IgA isotypes (Kappa or Lambda) at lower frequencies. This distribution is consistent with classical literature data, where IgG accounts for more than 60% of isotypes in MGUS and remains predominant in MM. The presence of rare isotypes or biclonal/triclonal forms (22.21% in our series) is noteworthy and slightly higher than in general series (often <10%), which could reflect an immunologically unstable background or prolonged antigenic stimulation due to autoimmune diseases.

The mean MC concentration was  $4.12 \pm 4.34$  g/L for the whole cohort, with a mean of 4.75 g/L in Group 1 and 4.13 g/L in Group 2. These values remain generally moderate, but some patients presented concentrations  $\geq 15$  g/L, which represents an important risk factor for progression in MGUS according to the Mayo Clinic model (1).

Prognostic assessment revealed that in Group 1, 63.63% of patients were classified as stage I (good prognosis) and 27.27% as stage III (poor prognosis). In Group 2, 64.70% had no risk factors for progression (low risk), 35.29% had a single risk factor (intermediate risk), and no patient presented all three major risk factors (high risk). This suggests that most patients in our cohort remain at low risk with a favorable prognosis, despite the autoimmune context. Nevertheless, it should be noted that most patients did not undergo  $\beta 2$ -microglobulin or free light chain (FLC) testing, which makes the prognostic evaluation incomplete.

According to some observational studies, the presence of MGUS could in some cases modulate the immune response, maintaining a transient immunological balance in patients with autoimmune diseases. However, no large-cohort study has conclusively confirmed a protective effect, and further longitudinal research is needed to assess the true prognostic impact of this interaction. Long-term follow-up and expansion of the cohort are required to confirm the actual prognostic value, identify potential evolutionary factors, and better understand the interplay

between monoclonal gammopathy and autoimmune disease.

The literature highlights that the monoclonal peak observed in MGUS can be either transient or persistent, with notable prognostic implications. According to Buadi et al. (Blood Cancer Journal, 2021), the absence of clonal bone marrow plasmacytosis is frequently associated with transient peaks, particularly in light IgG forms, often incidentally discovered (23). Furthermore, Kyle and Rajkumar (Immunological Reviews, 2003) report that such peaks may disappear or fluctuate in the context of concomitant inflammatory, infectious, or thrombotic diseases, making their diagnostic interpretation sometimes challenging (24). Studies such as Cesana et al. (2002) also report that the absence of clonal bone marrow plasmacytosis is often linked to transient monoclonal peaks, especially in IgG forms. These peaks may disappear or fluctuate depending on the evolution of concomitant inflammatory or thrombotic diseases, further complicating diagnostic interpretation (4).

### Study limitations:

The retrospective nature of our study and the limited number of specialized tests (e.g., free light chain assay,  $\beta 2$ -microglobulin measurement, Bence Jones protein detection) represent methodological limitations. A broader longitudinal follow-up and cytogenetic analyses (e.g., translocations involving the 14q32 region [IgH heavy chain gene], deletions of the short arm of chromosome 17 [17p], the locus of the TP53 gene) would help clarify the evolutionary mechanisms toward malignant forms.

### Perspectives:

It would be of interest to monitor the evolution of MGUS patients with autoimmune diseases to determine whether they present a higher transformation rate to MM. Furthermore, analysis of cytokine profiles (IL-6, TNF- $\alpha$ ) and gene expression signatures of autoimmune-associated plasma cells could open new perspectives for the development of targeted or preventive therapeutic strategies.

### Conclusion:

Our retrospective study conducted on a cohort of 162 patients with monoclonal gammopathies associated with autoimmune diseases (AID) highlights several major findings. On one hand, monoclonal gammopathy of undetermined significance (MGUS) remains the most frequent form, occurring at an earlier age than reported in classical series of isolated gammopathies. On the

other hand, rheumatoid arthritis, Sjögren's syndrome, and systemic lupus erythematosus emerge as the most frequently associated autoimmune diseases.

From an immunological perspective, IgG isotypes predominate, and the monoclonal component (MC) concentration remains moderate in most cases, conferring an overall favorable prognostic profile. This good prognosis may be attributed to close immunological monitoring enabling earlier diagnosis, but it may also be overestimated due to the limited sample size.

Finally, some recent data suggest that the presence of MGUS could, in certain cases, favorably modulate the course of some autoimmune diseases—a compelling hypothesis that nevertheless requires confirmation through larger-scale prospective studies.

Regular, long-term clinical and immunological follow-up is essential for these patients, in order to better define evolutionary trajectories and refine prognostic stratification.

### Conflict of interest:

The authors declare that the research was conducted without any conflict of interest.

### Bibliography:

1. Rajkumar SV. Multiple myeloma: 2020 update on diagnosis, risk-stratification and management. *Am J Hematol.* mai 2020;95(5):548-67.
2. Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol.* nov 2014;15(12):e538-48.
3. Palumbo A, Avet-Loiseau H, Oliva S, Lokhorst HM, Goldschmidt H, Rosinol L, et al. Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group. *J Clin Oncol.* 10 sept 2015;33(26):2863-9.
4. Cesana C, Klersy C, Barbarano L, Nosari AM, Crugnola M, Pungolino E, et al. Prognostic Factors for Malignant Transformation in Monoclonal Gammopathy of Undetermined Significance and Smoldering Multiple Myeloma. *J Clin Oncol.* 15 mars 2002;20(6):1625-34.
5. Shimanovsky A, Alvarez Argote J, Murali S, Dasanu CA. Autoimmune manifestations in patients with multiple myeloma and monoclonal gammopathy of undetermined significance. *BBA Clin.* déc 2016;6:12-8.
6. Liu H, Li P, Li K, Zhou Z, Zhou Y, Leng X, et al. Monoclonal gammopathy in autoimmune diseases: Analysis and follow-up of 160 cases in a tertiary center in China. *Clin Immunol.* janv 2022;234:108909.
7. Harmer D, Falank C, Reagan MR. Interleukin-6 Interweaves the Bone Marrow Microenvironment, Bone Loss, and Multiple Myeloma. *Front Endocrinol.* 8 janv 2019;9:788.
8. Dispenzieri A, Kyle RA, Katzmann JA, Therneau TM, Larson D, Benson J, et al. Immunoglobulin free light chain ratio is an independent risk factor for progression of smoldering (asymptomatic) multiple myeloma. *Blood.* 15 janv 2008;111(2):785-9.
9. Kumar S, Fonseca R, Ketterling RP, Dispenzieri A, Lacy MQ, Gertz MA, et al. Trisomies in multiple myeloma: impact on survival in patients with high-risk cytogenetics. *Blood.* 1 mars 2012;119(9):2100-5.
10. Chretien ML, Corre J, Lauwers-Cances V, Magrangeas F, Cleynen A, Yon E, et al. Understanding the role of hyperdiploidy in myeloma prognosis: which trisomies really matter? *Blood.* 17 déc 2015;126(25):2713-9.
11. Kyle RA, Rajkumar SV. Multiple Myeloma. *N Engl J Med.* 28 oct 2004;351(18):1860-73.
12. Liu H, Li P, Li K, Zhou Z, Zhou Y, Leng X, et al. Monoclonal gammopathy in autoimmune diseases: Analysis and follow-up of 160 cases in a tertiary center in China. *Clin Immunol.* janv 2022;234:108909.
13. Kyle RA, Therneau TM, Rajkumar SV, Larson DR, Plevak MF, Offord JR, et al. Prevalence of Monoclonal Gammopathy of Undetermined Significance. *N Engl J Med.* 30 mars 2006;354(13):1362-9.
14. Ferreri AJM, Reni M. Prognostic Factors in Primary Central Nervous System Lymphomas. *Hematol Oncol Clin North Am.* août 2005;19(4):629-49.
15. Landgren O, Kyle RA, Pfeiffer RM, Katzmann JA, Caporaso NE, Hayes RB, et al. Monoclonal gammopathy of undetermined significance (MGUS) consistently precedes multiple myeloma: a prospective study. *Blood.* 28 mai 2009;113(22):5412-7.

16. Arnaud L. Épidémiologie du lupus systémique : des approches traditionnelles aux mégadonnées. Bull Académie Natl Médecine. janv 2022;206(1):17-22.
17. Baecklund E, Smedby KE, Sutton LA, Askling J, Rosenquist R. Lymphoma development in patients with autoimmune and inflammatory disorders – What are the driving forces? Semin Cancer Biol. févr 2014;24:61-70.
18. Almutairi K, Nossent J, Preen D, Keen H, Inderjeeth C. The global prevalence of rheumatoid arthritis: a meta-analysis based on a systematic review. Rheumatol Int. mai 2021;41(5):863-77.
19. Solans-Laqué R, López-Hernandez A, Angel Bosch-Gil J, Palacios A, Campillo M, Vilardell-Tarres M. Risk, Predictors, and Clinical Characteristics of Lymphoma Development in Primary Sjögren's Syndrome. Semin Arthritis Rheum. déc 2011;41(3):415-23.
20. Zucchi D, Houbaida Y, Tani C, Del Giudice ML, Stagnaro C, Elefante E, et al. ABS0523 MONOCLONAL GAMMOPATHY IN SYSTEMIC LUPUS ERYTHEMATOSUS: CHARACTERIZATION, CLINICAL FEATURES, AND RISK OF PROGRESSION. Ann Rheum Dis. juin 2025;84:2210-1.
21. Shimanovsky A, Alvarez Argote J, Murali S, Dasanu CA. Autoimmune manifestations in patients with multiple myeloma and monoclonal gammopathy of undetermined significance. BBA Clin. déc 2016;6:12-8.
22. Rajkumar SV, Kyle RA, Therneau TM, Melton LJ, Bradwell AR, Clark RJ, et al. Serum free light chain ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance. Blood. 1 août 2005;106(3):812-7.
23. Pang L, Rajkumar SV, Kapoor P, Buadi F, Dispenzieri A, Gertz M, et al. Prognosis of young patients with monoclonal gammopathy of undetermined significance (MGUS). Blood Cancer J. 1 févr 2021;11(2):26.
24. Kyle RA, Rajkumar SV. Monoclonal gammopathies of undetermined significance: a review. Immunol Rev. août 2003;194(1):112-39.