Research Article

Characterizing Monoclonal Gammopathies in an East Moroccan Population: University Hospital Findings

Oussama Grari[1,2*], Kaoutar Benaissa[1,2], Nisma Douzi[1,2], Imad-eddine Elkhamlichi[1,2], Amina Himri[1,2], Dounia Elmoujtahide[1,2], El-houcine Sebbar[1,2], Mohammed Choukri[1,2]

[1*]*Faculty of Medicine and Pharmacy, Mohammed I University, Oujda, Morocco*
[2*]*Biochemistry Department, Mohammed VI University Hospital, Oujda, Morocco*

Article Info

Author of correspondence:
Dr. Grari Oussama
Medical Resident in laboratory medicine, Central Laboratory, Mohammed VI University Hospital of Oujda
E-mail: oussama.grari@ump.ac.ma
Tel.: +212650336765
ORCID: 0000-0003-2301-4491
Address:
Thami Jilali Avenue 60050,Oujda, Morocco

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Abstract

Background
Monoclonal gammopathies (MG) are frequent, especially among older people. This study aims to establish the features and etiologies of MG detected over seven years in the Biochemistry department of Mohammed VI University Hospital in Morocco.

Methods
The study was performed from Jan 1, 2016, to Sept 1, 2023, and involved 224 patients residing in east Morocco. The diagnosis of MG was conducted through capillary zone electrophoresis, followed by confirmation through immunofixation.

Results
The study included 224 patients, with an average age at diagnosis of 65.91 years. There were 122 (54.46%) males and 102 (45.54%) females, for a sex ratio of 1.19. In terms of immunoglobulin isotypes, IgG was found to be the most common monoclonal protein (59.82%), followed by IgA (19.64%) and IgM (6.71%). Furthermore, 11.6% of cases had exclusive free light chain (FLC) secretion, and 2.23% had biclonal gammopathy. The distribution of diagnoses in our study included multiple myeloma (MM) (78.57%), lymphoma (5.35%), plasma cell leukemia (4.02%), Waldenström macroglobulinemia (WM) (3.57%), and MGUS (1.79%).

Conclusions
Our study noted the high frequency of MM over MGUS. Several factors could contribute to this prevalence, including variations in healthcare access, demographic characteristics, and potentially other elements that warrant further investigation.

Abbreviations
AL amyloidosis: light chain amyloidosis; CRP: C-reactive protein; FLC: free light chains; IQR: interquartile range; LDH: lactate dehydrogenase; MG: monoclonal gammopathies; MGUS: monoclonal gammopathy of undetermined significance; MM: multiple myeloma; sFLC: Serum free light chain; SIFE: serum immunofixation electrophoresis; SMM: smoldering multiple myeloma; SPE: serum protein electrophoresis; UPE: urine protein electrophoresis; WM:

Waldenström macroglobulinemia.

Introduction

MG are a group of diseases that affect the bone marrow. They are caused by the clonal proliferation (one clone) of plasma cells that overproduce immunoglobulins or fragments, also called paraprotein or M-protein [1]. The released proteins serve as diagnostic markers for disease identification and quantitative biomarkers for monitoring disease progression and therapeutic response [2]. MG represents a heterogeneous and complex group of conditions with different manifestations, therapy, and prognosis. A plasma cell dyscrasia or a B-cell lymphoproliferative disorder could cause MG. Its severity varies from typically benign and asymptomatic MGUS to incurable MM and AL amyloidosis [3]. MG are a laboratory-based diagnosis that is becoming more common in older people. The primary methods include serum protein electrophoresis (SPE) and urine protein electrophoresis (UPE), which detect and quantify M-proteins in serum and urine. Immunofixation electrophoresis (IFE) is often employed to confirm the presence and type of M-protein, offering greater sensitivity than SPE alone. Serum free light chain (sFLC) assays are crucial in diagnosing, monitoring, and prognosticating MG, including MM and other plasma cell dyscrasias [4,5]. Our study aims to describe the epidemiological, biochemical, and hematological profiles of MG diagnosed in the Biochemistry department of Mohammed VI University Hospital of Oujda over more than seven years.

Material and methods

The study was a retrospective investigation conducted at Mohammed VI Teaching Hospital in Oujda. It included all patients diagnosed with SIFE positivity between Jan 1, 2016, and Sept 1, 2023. The biochemistry laboratory's immunofixation register was used for this purpose. Data collected from electronic medical records comprised age, gender, light and heavy chain isotypes, measurement of monoclonal protein, total protein, calcium, creatinine, urea, C-reactive protein (CRP), β2 microglobulin, lactate dehydrogenase (LDH), κ/λ ratio, complete blood count, blood smear, and bone marrow aspiration smear. Capillarys 2 and 3 (Sebia) and HYDRASYS 2 SCAN FOCUSING (Sebia) were used for serum protein capillary electrophoresis and immunofixation assays. In cases of light chain-only gammopathy, we screened for both IgD and IgE.

Urinary immunofixation was assessed using HYDRASYS 2 SCAN FOCUSING (Sebia) Gel electrophoresis. We evaluated the biochemical parameters with the Abbott Architect ci8200 and Alinity systems. For diagnosis, we adhered to the International Myeloma Working Group (IMWG) updated criteria for MM, SMM, and MGUS [6]. Advanced statistical analyses were conducted to compare demographic and clinical characteristics between groups. Categorical variables were compared using chi-square tests, and continuous variables were compared using ANOVA. All data were collected using Microsoft Excel, and statistical analysis was performed using SPSS Statistics Version 21.0 (IBM Corporation, Armonk, NY, USA).

Results

314 patients were initially considered for this study because they had positive monoclonal immunoglobulin in SIFE. Of these, 90 patients were excluded since no diagnosis was attributed. Therefore, 224 patients were ultimately included in the analysis. Additionally, some patients lacked ß2 microglobulin, LDH, or M protein quantification data. While these patients were included in the overall study, they were excluded from the calculation of statistical parameters for these three variables in Table 1. There were 122 (54.46%) men and 102 (45.54%) women, for a sex ratio of 1.19. The mean age at diagnosis was 65.91 ± 11.81 years, with extremes ranging from 32 to 95 years old. Additionally, individuals aged 40 years and above constituted 89.28% of all diagnosed patients. All patients were of Moroccan nationality and were from the country's eastern region. The essential characteristics of the population diagnosed with MG are shown in Table 1. In our study, 92.85% of patients (n=208) showed a monoclonal peak. In 78.37% (n=163) of cases, the peak was in the γ globulin region, 21.15% (n=44) in the β globulin region, and 0.48% (n=1) in the α region. In terms of immunoglobulin isotypes, IgG was the most common monoclonal protein (59.82%), followed by IgA (19.64%) and IgM (6.71%). Furthermore, the only secretion of FLC was seen in 11.6% of the cases, while 2.23% exhibited biclonal gammopathy. The distribution of the monoclonal proteins found in this investigation is shown in Table 2. The distribution of the patients' diagnoses in our study was as follows: MM (78.57%), lymphoma (5.35%), plasma cell leukemia (4.02%), WM (3.57%), and MGUS (1.79%). Table 3 lists the additional clinical diagnosis, and Table 4 provides the isotype distribution for each diagnosis.For 133 individuals, urinary immunofixation was conducted, and in 95 (71.42%) of those cases, the results were positive. We conducted advanced statistical analyses to assess the differences in demographic and clinical characteristics across different types of MG. A chi-square test was performed to evaluate the association between sex and diagnosis, yielding a chi-square value of 8.024 and a p-value of 0.431, indicating no statistically significant difference in sex distribution across different diagnoses. Additionally, an ANOVA test was conducted to compare the mean age across different diagnoses, resulting in an F-statistic of 0.623 and a p-value of 0.758, suggesting no statistically significant difference in age distribution among the different MG. These findings indicate that sex and age are not significantly different across the various diagnostic categories in our study cohort.

Table 1: Principal characteristics of the 224 participants in the study.

	Mean ± SD or Median[IQR]	Minimum	Maximum	CI 95%	*n*
Age (years)	65.91±11.81	32	95	64.35-67.46	224
Male					122 (54.46%)
Female					102 (45.54%)
Total protein (*N*: 60-80 g/L)	81[33.25]	41	164	75.54-86.45	224
C-reactive protein CRP (*N*: 0-5 mg/L)	10.55[37.31]	0.13	530.49	7.21-13.80	224
Calcium (*N*: 84-102 mg/L)	91[15.25]	62	176	90.0-94.0	224
Creatinine (*N* : M : 7.2-12.5mg/L ; F : 5.7-11.1mg/L)	M 11.29 [16.56] / F 8.55 [13.85]	M 3.45 / F 5.01	M 252 / F 231	M 7.61-14.97 / F 8.00-9.46	224
Urea (*N*: 0.15-0.45 g/L)	0.41[0.605]	0.14	3.85	0.36-0.47	224
LDH (*N*: 125-243 U/L)	220.0[167.0]	52	3325	208.95-237.0	217
β2 microglobulin (*N*: 0.97-2.64 mg/L)	5.78[8.79]	0.60	90.55	4.66-6.99	136
M protein Quantification (g/L)	19.35[29.7]	2.6	100	14.95-23.90	124
κ/λ Ratio	1.94[11.46]	0.0	580	1.45-2.83	105

CI 95%: 95% confidence interval; F: female; IQR: interquartile range; M: male; SD: standard deviation, n: total count
The 95% CI represents the range within which we can be 95% confident that the true mean (for normally distributed data) or median (for non-normally distributed data) lies.

Table 2: Isotype distribution.

	N	%
IgG	**134**	**59.82**
κ	82	36.60
λ	52	23.22
IgA	**44**	**19.64**
κ	18	8.04
λ	26	11.60
IgM	**15**	**6.71**
κ	14	6.26
λ	1	0.45
FLC	**26**	**11.6**
κ	8	3.57
λ	18	8.03
Biclonal	**5**	**2.23**
Total	**224**	**100**

Table 3: The distribution of etiologies in the study's patients.

	N	%
MM	176	78.57
Lymphoma	12	5.35
Plasma Cell Leukemia	9	4.02
WM	8	3.57
MGUS	4	1.79
Chronic lymphocytic leukemia	4	1.79
Plasmocytoma	3	1.34
Unclassed	8	3.57
Total	224	100

Table 4: Isotype distribution for each diagnosis.

Diagnosis	IgG	IgA	IgM	FLC	Biclonal	*n*
MM	111	41	1	21	2	176
Lymphoma	5	0	4	2	1	12
Plasma Cell Leukemia	4	1	0	3	1	9
WM	0	0	8	0	0	8
MGUS	3	0	0	0	1	4
Chronic lymphocytic leukemia	3	0	1	0	0	4
Plasmocytoma	2	1	0	0	0	3
Unclassed	6	1	1	0	0	8
Total	134	44	15	26	5	224

Patients with MM

MM was found in 176 participants overall in our study. Of them, 79 (44.89%) were women and 97 (55.11%) were men. The mean age of the patients was 66.56 ± 11.58 years, with ages ranging from 32 to 95 years. The most frequent isotype observed in the study was IgG, accounting for 63.06% (n=111) of the cases, followed by IgA at 23.30% (n=41), FLC at 11.93% (n=21), biclonal at 1.14% (n=2), and IgM at 0.57% (n=1). We noticed 88.07% (n=155) were anemic, and 6.82% (n=12) had rouleaux development at the blood smear. The median calcium level was 90.50 mg/L [IQR: 17], ranging from 62 to 176 mg/L. 115 patients underwent urinary immunofixation; 95 instances (72.17%) had positive results.

Discussion

The study aimed to clarify the features of MG in Moroccan patients and compare our results with those of previous studies. This study's data collection was probably not exhaustive because some patient categories were not included in the analysis. The study excluded patients with incomplete medical records, those without a confirmed diagnosis, and those who did not receive follow-up care in a hospital setting. This exclusionary strategy was used to guarantee the validity and consistency of the data collected, but it might not fully represent all patients with MG. In line with previous research [7–9], the patients in our study ranged in age from 32 to 96 years old, with a mean age of 66. This alignment supports the notion that older people are the target group of MG, as it can occur in up to 8% of the aged population [10]. In children, MG is rarely seen [11]. As the population ages and more advanced electrophoresis methods are developed, MG cases will likely increase gradually in the coming years. Moreover, our study's male predominance is consistent with the data published in the literature [12,13]. We observed that the IgG isotype predominated in our study, with IgA and IgM following suit. Comparable isotype distributions have been documented in cohorts originating from Morocco [14], Spain [15], and Tunisia [8]. This uniformity among neighboring nations highlights the regional similarity of MG patterns. Table 5 compares our dataset's monoclonal protein isotype distribution with results from other studies. Biclonal gammopathies accounted for only 2% of the cases in our study, reflecting the low prevalence reported in the literature [16]. Nonetheless, in other global investigations, the sequence of M-protein isotypes is often IgG, followed by IgM and then IgA. The potential explanation for

this variation could be the impact of ethnic differences on the expression patterns of these isotypes. Additionally, challenges in detecting IgA, particularly in minimal concentrations due to potential overlap with standard protein electrophoresis bands, especially the β1- and β2-globulins fractions, could elucidate the differences observed in comparison to the second most prevalent M-protein isotype documented in the literature.

Table 5: Comparison of our dataset's monoclonal protein isotype distribution with results from other studies.

	Our data (n=224)	Ouzzif et al [14] (n=261)	El Maataoui et al [17] (n=117)	Belouni et al [7] (n=2121)	Mseddi et al [8] (n=288)	Bergon et al [15] (n=537)	Decaux et al [12] (n=1051)	Tamimi et al [13] (n=416)
IgG	59.82	54.58	55.4	60.91	51,7	55.8	48,6	60
IgA	19.64	14.74	19.2	17.91	20,8	20.8	8,1	5.5
IgM	6.71	10.75	3.6	6.6	8,7	13.6	30,3	10
IgD	0	0	2.4	1.03	1	0.4	0	0
IgE	0	0	0	0.09	0	0	0	0
FLC (κ or λ)	11.6	0	17	10.46	13,6	6.4	3,7	24.3
Biclonal	2.23	2.79	2.4	2.82	2,1	3	9,3	0
Tricolonal	0	0	0	0.14	0	0	0	0

A significant distinction from other studies arises in the diagnosis distribution of our population, where the most prevalent diagnosis is MM rather than MGUS (Table 6). These findings contradict the existing literature but are consistent with the findings of two prior investigations conducted in Morocco [14,17]. These investigations also found a similar pattern, implying that the frequency of MM outweighing MGUS is a recurring trend in the Moroccan community. Furthermore, it is important to mention that despite our extensive research, we identified no cases of SMM among our study participants. This lack is remarkable, especially given the findings of the iStopp MM study [18], which included a large cohort of nearly 75,000 people. Their findings revealed a SMM frequency of 0.53% among people aged 40 and up. This difference in distribution between MM and MGUS in our East Moroccan study population can be attributed to a complex interplay of factors. Firstly, several limitations and potential biases inherent in this study's design and execution must be acknowledged when interpreting its findings. This investigation's retrospective nature introduces inherent limitations. Relying on preexisting data may lead to incomplete or missing information and potential selection biases. Despite efforts to mitigate these issues through rigorous data collection and inclusion criteria, the possibility of residual confounding cannot be entirely excluded. Additionally, healthcare system-related issues might have contributed to this distribution disparity. It's plausible that only symptomatic patients, more likely to exhibit abnormal SPE and SIFE results, were included in our study due to the nature of healthcare access or utilization patterns in the region. As a result, asymptomatic individuals with MGUS might have been underrepresented. These factors underscore the need for cautious interpretation of our findings and highlight the importance of considering potential biases and limitations when extrapolating results to the broader population. Future studies with larger and more diverse cohorts and efforts to address healthcare access barriers will be crucial for obtaining a comprehensive understanding of the prevalence and distribution of MG in the East Moroccan population. Other factors contributing to these findings could be demographic traits and regional variances in genetic factors, forming a different disease profile in the East Moroccan population. Furthermore, unique environmental exposures to these places may impact the development of plasma cell disorders, including MM and MGUS. Differences in diagnosis practices, criteria, and awareness can also impact the observed distribution of these diseases.

Table 6: Comparison of diagnoses in our dataset with findings from other studies.

	Our data (n=224)	Ouzzif et al [14] (n=261)	El Maataoui et al [17] (n=117)	Ouzzif et al [9] (n= 443)	Mseddi et al [8] (n=288)	Bergon et al [15] (n=537)	Decaux et al [12] (n=1051)	Tamimi et al [13] (n=416)
MM	78.57	52.77	82.1	45.65	59.26	31.3	14.1	14.6
MGUS	1.79	34.92	2.6	39.05	27.04	54.1	64.1	68
WM	3.57	3.97	1.7	5.58	4.81	2	8.7	4
Plasma Cell leukemia	4.02	0	1.7	1.86	0	0	0	0
Plasmocytoma	1.34	0.79	8.5	0.62	0	2.2	0.3	0
Lymphoma	5.35	3.97	2.6	3.51	3.12	6.3	4.2	6.5
Chronic lymphocytic leukemia	1.79	1.59	0.9	2.48	1.38	3.2	2.1	2.1

Conclusion

The MG profile reported in our group differs from established patterns in the literature, particularly in the diagnosis distribution. The distinctive features of diagnostic prevalence in our East and North Moroccan sample highlight the need for a more comprehensive knowledge of disease dynamics in this population. Further research should dive into the complexities of these disparities, elucidating the regional elements that contribute to the observed differences in disease profiles. Given that the clinical laboratory is the only setting in which all M-protein patients are followed, we believe it should play a significant role in the study of MG, serving as a focal point for comprehensive investigations and contributing to a more holistic understanding of these disorders.

Conflict of interest disclosure

The authors have no conflicts of interest to disclose.

Ethical Approval

The research studies involving human subjects strictly adhered to the ethical standards outlined in the 1964 Helsinki Declaration, as established by the relevant institutional and national research committees.

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