

Epidemiology of monoclonal gammopathy in Morocco- A hospital-based study

Running Head: Monoclonal gammopathy

Zhor Ouzzif¹, KAMAL DOGHMI¹, nezha messaoudi¹, Sanae Bouhsain¹, SAMIRA EL MACHTANI IDRISSI¹, Asmaa Biaz¹, Achraf Rachid¹, Abdellah Dami¹, Ahmed BEZZA¹, and AISSAM EL MAATAOUI²

¹Hopital Militaire d'Instruction Mohammed V

²Universite Ibn Zohr

October 24, 2022

Abstract

Introduction: Monoclonal gammopathies are a group of disorders associated with monoclonal proliferation of plasma cells that produces a monoclonal protein. To describe the epidemiological and immunochemical characteristics of monoclonal gammopathies diagnosed during a nineteen-year period in a Moroccan teaching hospital was the main objective of this study. **Methods:** This study was performed from January 2000 to August 2019. It was a retrospective study that included of 545 Moroccan patients with monoclonal gammopathy. **Results:** The patients who participated in the study, 374 (68.6%) were male and 171(31.4%) were female, with a mean \pm SD age of 62.24 ± 13.14 years. The most frequent reasons for admission were bone pain (41.60%), renal failure (19.08%), alteration of the general condition (12.21%) and anemia (10.69). Plasma cell proliferative disorders in our study were as follow, multiple myeloma (MM) (45.65%), Monoclonal gammopathies of undetermined significance (MGUS) (39.05%), Waldenstrom's macroglobulinemia(5.58%), Lymphoma (2.27%+1.2%), Chronic Lymphocytic Leukemia (2.48%), Plasma cell leukemia (1.86%), Plasmacytoma (0.62%), POEMS syndrome (0.41%), and Amyloidosis (0.84%). The most frequent isotypes in MM were the IgG κ (62) 36.5%, IgG λ (52)30.6%, IgA κ (27)15.9% and the IgA λ (19)11.2%. It is also worthy of note, that Free light chain MM represents 20% of all cases of MM. **Conclusions:** This is the largest Moroccan cohort, it included 545 patients. The results of this study point to the need for an early diagnosis of monoclonal gammopathies in the Moroccan population

Title: Epidemiology of monoclonal gammopathy in Morocco- A hospital-based study

Running Head: Monoclonal gammopathy

Authors:

Z. OUZZIF¹, K. DOGHMI¹, N. MESSAOUDI¹, S. BOUHSAIN¹, S. EL MACHTANI¹, A. BIAZ¹, A. RACHID¹, A. DAMI¹, A. BEZZA¹, A. EL MAATAOUI ^{2**}

1. The Military Hospital Instruction Mohamed V / Mohamed V University, Faculty of Medicine and Pharmacy, Rabat, Morocco.
2. Ibn Zohr University, Agadir teaching hospital, Faculty of Medicine and Pharmacy, Clinical Chemistry Department-Agadir, Morocco.

Authors e-mails:

Zohra OUZZIF zahra.ouzzif@yahoo.com

Kamal DOGHMI kdoghmi@gmail.com

Nezha MESSAOUDI messaoudi.nezha@yahoo.fr

Sanae BOUHSAIN bouhsainsanae1@yahoo.fr

Samira EL MACHTANI elmachtaniidrissi@yahoo.com

Asmae BIAZ biazasmaa@yahoo.fr

Achraf RACHID rachid.achraf1@gmail.com

Abdallah DAMI abdami@yahoo.fr

Ahmed BEZZA ahmedbezza239@gmail.com

Aissam EL MAATAOUI a.elmaataoui@uiz.ac.ma

****Corresponding author**

AISSAM EL MAATAOUI PharmD PhD

E-mail : a.elmaataoui@uiz.ac.ma

Address: Clinical chemistry department,

Faculty of medicine and pharmacy, Agadir –Morocco

Ethics approval

The local ethics committee in Mohamed V university, faculty of medicine and pharmacy Rabat approved this study.

Patients were recruited and enrolled at Mohamed V teaching hospital in rabat. Written informed consent procedures, conforms to the ethical guidelines of the declaration of Helsinki and was approved by the ethics committee in Mohamed V university, faculty of medicine and pharmacy, Rabat-Morocco.

ABSTRACT

Introduction: Monoclonal gammopathies are a group of disorders associated with monoclonal proliferation of plasma cells that produces a monoclonal protein. To describe the epidemiological and immunochemical characteristics of monoclonal gammopathies diagnosed during a nineteen-year period in a Moroccan teaching hospital was the main objective of this study.

Methods : This study was performed from January 2000 to August 2019. It was a retrospective study that included of 545 Moroccan patients with monoclonal gammopathy.

Results: The patients who participated in the study, 374 (68.6%) were male and 171(31.4%) were female, with a mean \pm SD age of 62.24 ± 13.14 years. The most frequent reasons for admission were bone pain (41,60%), renal failure (19.08%), alteration of the general condition (12.21%) and anemia (10.69). Plasma cell proliferative disorders in our study were as follow, multiple myeloma (MM) (45.65%), Monoclonal gammopathies of undetermined significance (MGUS) (39.05%), Waldenstrom's macroglobulinemia(5.58%), Lymphoma (2.27%+1.2%), Chronic Lymphocytic Leukemia (2.48%), Plasma cell leukemia (1.86%), Plasmacytoma (0.62%), POEMS syndrome (0.41%), and Amyloidosis (0.84%). The most frequent isotypes in MM were the IgG κ (62) 36.5%, IgG λ (52)30.6%, IgA κ (27)15.9% and the IgA λ (19)11.2%. It is also worthy of note, that Free light chain MM represents 20% of all cases of MM.

Conclusions: This is the largest Moroccan cohort, it included 545 patients. The results of this study point to the need for an early diagnosis of monoclonal gammopathies in the Moroccan population

Key words

Epidemiology, monoclonal gammopathy, Morocco, Monoclonal protein.

INTRODUCTION

Monoclonal gammopathies (MG) represent a group of pathologies characterized by the clonal proliferation of plasma cells that produce a paraprotein or monoclonal protein (M-protein). The generalization of the screening of the MG by serum protein electrophoresis, which represents a heterogeneous group of diseases, and especially the evolution of imaging and radiology techniques, have made possible to diagnose MG frequently and at early stages. The most important risk factors are age, gender and black race. Several studies have reported a mean age of patients at the time of diagnosis of monoclonal gammopathy of 68 years, most patients (99%) were over 40 years old at the time of diagnosis^{1,2}. Regarding gender, monoclonal gammopathies affect men more than women. In a retrospective study, the age-adjusted incidence of monoclonal gammopathies was 10.3 and 8.6 per 100,000 in men and women, respectively³. Finally, for the black race, in a study found that the prevalence of monoclonal gammopathies of undetermined significance (MGUS) in men from Ghana (5.84% (95% CI, 4.27-7.40)) was significantly higher than the prevalence in white men from Olmsted in the USA (2.97%, (95% CI, 2.59-3.34))^{4,5}.

Monoclonal gammopathy of undetermined signification (MGUS), is defined by the production of monoclonal protein without any systemic effect. It represents the early stage of the multiple myeloma (malignant stage). MGUS accounts for 3% of MG in patients over 50 years of age⁶. In general, MGUS will progress to hematologic malignancies including multiple myeloma or MM, which progresses at a rate of 1% per year⁷.

MM represents 10% of hematologic malignancies in general, the median age at diagnosis is estimated to be 70 years, and it affects more men (7 per 100,000) than women (4.5 per 100,000), blacks more than whites, thus, the highest prevalence rate is observed in African Americans, particularly in those aged 80-84 years and older⁶. Furthermore, the most frequently observed primary immunoglobulin heavy chain (IgH) translocation was t(11;14), found in 16% of patients in the absence of trisomies, and in 3% in the presence of trisomies⁸. Nevertheless, the following cytogenetic abnormalities, t(4;14), t(14;16), t(14;20), del(17p), gain 1q, or p53 mutation are associated with high risk MM⁸.

To describe the epidemiological and immunochemical characteristics of monoclonal gammopathies diagnosed during a nineteen-year period in a Moroccan teaching hospital was the main objective of this study.

MATERIALS AND METHODS

Patient selection

The study was carried out over a period of 19 years, between January 2000 and August 2019. A retrospective study that included of 545 Moroccan patients with monoclonal gammopathy detected through a serum electrophoresis, urine and serum immunofixations. Urine immunofixation is important in defining the nature of the band and in distinguishing between Bence Jones protein and an intact monoclonal protein originating from the serum. The patients who had monoclonal protein were included. But, only 484 patients were selected, they have had complete medical records at the clinical departments.

Methods

Blood samples were collected using serum dry tubes, the samples left to clot for one hour before centrifugation at 1000 RPM for 15 minutes. Total protein (g/L), C-reactive protein CRP[®] (mg/l), Calcium (mg/l), creatinine (mg/l), urea(g/l) were measured with Dimension Rxl Siemens analyzer[®]. The β_2 -microglobulin and the immunoglobulins (IgA, IgG and IgM) was measured with an immunonephelometer analyzers from Dade Behring BN II [®]. The Sedimentation rate was measured at the first hour (mm) (SRFH). Hemoglobin (Hb) (g/dl) was measured with the Beckman Coulter hematology analyzers (reference values: In woman Hb \geq 12 g/dl, in men Hb \geq 13 g/dl). Urine immunofixation was performed in urine samples collected for 24 hours.

Protein electrophoresis was performed on all samples with capillary electrophoresis system from Sebia[®]. Immunofixation was performed in the following situations when an abnormal serum protein electrophoresis was defined by the presence of a quantifiable Monoclonal spike, hypogammaglobulinemia and a fuzzy band. Furthermore, when we have an increased numbers of abnormal, atypical or immature plasma cells in the bone marrow, hypercalcemia, histological proof of plasmacytoma and high SRFH.

Serum and urine immunofixation were performed on Hydrasys Sebia®. Patient records have been reviewed for clinical history and the monoclonal protein type. The diagnosis of monoclonal gammopathies is based on the presence of an increase in the number of plasma cells and/or immature and dystrophic plasma cells in the marrow, the presence of histological evidence of plasmacytoma, the presence of monoclonal protein in the serum and urine and/or bone lesions.

Statistical analysis

The statistical analysis was carried out by a software SPSS 13.0 of IBM for windows. the continuous parameters, the results were expressed by the Mean \pm standard deviation (SD).

RESULTS

The baseline characteristics of the study participants are as follow. The study included 374 (68.6%) men and 171 (31.4%) women, the mean \pm SD ages were 62.24 ± 13.14 years. The mean \pm SD years age for the MM, MGUS, WM, LLMM, KLMM and the POEMS (Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome) were respectively of 61.70 ± 11.66 , 63.64 ± 13.66 , 61.71 ± 13.35 , 60.57 ± 10.90 , 56.50 ± 12.83 and 45.50 ± 2.12 . regarding ethnic origin, all patients were of Caucasian origin, from the twelve regions of the Kingdom of Morocco. The most frequent reasons for admission were the bone pain (41.60%), the renal failure (19.08%), the alteration of the general condition (12.21%) and anaemia (10.69) (Table1). Plasma cell proliferative disorders in our study were as follow, MM (45.65%), Monoclonal gammopathies of undetermined significance (MGUS) (39.05%), Waldenstrom's macroglobulinemia (5.58%), Lymphoma (2.27%+1.2%), Chronic Lymphocytic Leukaemia (2.48%), Plasma cell leukaemia (1.86%), Plasmacytoma (0.62%), POEMS syndrome (0.41%), and Amyloidosis (0.84%) (Table 2).

The estimated glomerular filtration rate (eGFR) in patients with MM was low compared to other monoclonal gammopathies, but the lowest eGFR were in patients with Free light chain MM, with more cases with kappa versus lambda light chain myeloma myeloma. The frequency of hypercalcemia was very high in patients with multiple myeloma and plasma cell leukaemia compared to other gammopathies. The kappa/Lambda ratio was highly elevated in patients with MM, plasma cell leukaemia, and plasmacytoma in comparison to the other MG. Even in patients with MGUS, the kappa/Lambda ratio was elevated.

The total protein level is highly increased in patients diagnosed with MM and WM and low in patients diagnosed with light chain MM. Low albumin concentration was found in patients with MM and plasma cell leukaemia. The SRFH was very high in patients with WM and MM. Furthermore, monoclonal protein levels were higher in patients with MM (38.21 ± 23.83), MW (33.31 ± 20.65) and MGUS (11.76 ± 6.96).

Concentrations of parameters used in the prognostic evaluation of monoclonal gammopathies (β_2 - microglobulin, CRP and LDH) were higher in patients with MM and MGUS respectively. Anaemia was more profound in patients with multiple myeloma in general (9.76 ± 2.21), and in patients with free light chains MM (LLMM (7.76 ± 1.12), KLMM (9.07 ± 1.81)), and Waldenstrom's macroglobulinemia (9.29 ± 2.15) (Table 3).

The isotype repartition by Plasma cell proliferative disorders in this study is given in table 4. The most frequent monoclonal proteins in MM were the IgG κ (62) 36.5%, IgG λ (52)30.6%, IgA κ (27)15.9% and the IgA λ (19)11.2%. It is also worthy of note, that Free light chain MM represents 20% of all cases of MM.

For the MGUS, the most frequent isotypes were the IgG κ (87) 46.27%, IgG λ (61)32.44%, IgA κ (4)2.13%, IGA λ (9)4.78% , IgM λ (5)2.66% and IgM κ (9)4.78%. Finally, the most frequent isotypes in Waldenström's macroglobulinemia were IgM κ (19)70.37%, IgM λ (7)25.93%, and an oligoclonal profil (1)3.70% (Table 4).

DISCUSSION

The study was carried out over a period of 19 years, between January 2000 and August 2019. The patients who were included in this study were 545 patients. To describe the epidemiological and immunochemical characteristics of monoclonal gammopathies diagnosed during a nineteen-year period in a Moroccan teaching hospital was the main objective of this study. The results of this study point to the need for an early diagnosis of monoclonal gammopathies in the Moroccan population. The mean \pm SD age at diagnosis of all MG was

62.24±13.14 years, and with a sex ratio male/female of 2.14. Our results are in agreement with the results of international studies confirming that GM is age-related and affects men more than women¹⁻³.

Plasma cell proliferative disorders in our study were as follow, MM 45.65% (n=221), MGUS 39.05% (n=189), WM 5.58% (n=27), plasmacytomas 5.58% (n=27), plasma cell leukaemia 0.62% (n=3). The most frequent diagnosis of MG in the European and American studies was MGUS^{9,10}. In contrast, the most frequent diagnosis of monoclonal gammopathies in our study and the studies from Maghreb countries (Algeria and Tunisia) was MM^{11,12}. This is due to the delay in diagnosis and the lack of serum protein electrophoresis in most of the hospitals in Maghreb countries. In a cross-sectional study Gupta et al have reported a low incidence of MGUS in Indians compared to blacks and whites populations¹³. This study included 3429 patients, only 49 (1.43%) had a diagnosis of MGUS at the time of diagnosis¹³.

In this study, the POEMS syndrome was diagnosed only in 2 patients (0.41%), POEMS syndrome is relatively rare, in a mayo clinic study only 99 cases were diagnosed¹⁴.

The κ/λ ratio was very high in patients with MM (25.04), plasma cell leukaemia (26.67), MGUS (2.06) and plasmacytoma (19.00). Indeed, in patient with MM, Belouni et al, Mseddi et al and the Mayo clinic¹⁰⁻¹² have found the kappa/Lambda ratio respectively of 14.9, 14.13 and 16. Nevertheless, normal κ/λ ratio does not exclude the presence of a monoclonal gammopathy according to Singh et al, and false negatives rates associated with lambda chain are higher than those for lesions with kappa chains¹⁵.

The mean concentrations of monoclonal peak were MM (38.21±23.83), MW (33.31±20.65) and MGUS (11.76±6.96), these results are very far from the means noted in the patients included in the Algerian study of Belouni et al (22.19±20.19 g/l)¹¹ and in the majority of the other series, this can be explained by the late diagnosis of the monoclonal gammopathies in our country, and the high frequency of MM in our study in comparison of the international studies^{9,10}. Furthermore, Monoclonal protein concentration was elevated in patients diagnosed with MW or MM compared to MGUS.

Anaemia was more profound in patients with free light chain MM, LLMM (7.76±1.12), KLMM (9.07±1.81). This may be explained by the high frequency of free light chain MM, and the delay in the diagnosis of our patients with MM.

The isotype repartition by plasma cell proliferative disorders is given in table 4. The most frequent monoclonal proteins in the group of patients with MM were the IgG κ (62) 36.5%, IgG λ (52) 30.6%, IgA κ (27) 15.9% and the IgA λ (19) 11.2%. Regarding the MGUS group, the most frequent isotypes were the IgG κ (87) 46.27%, IgG λ (61) 32.44%, IgA κ (4) 2.13%, IgA λ (9) 4.78%, IgM λ (5) 2.66% and IgM κ (9) 4.78%. The same results were reported in the study of Landgren et al, the most frequent isotypes by race/ethnicity were IgG % (n) 76.1 (71), IgA 5.2 (5), IgM 2.7 (3) in black, IgG 68.1 (150), IgA 9.7 (12), IgM 15.4 (34) in whites and IgG 63.1 (29) IgA 16.7 (8) IgM 7.4 (6) in Mexican Americans¹⁶.

Finally, the most frequent isotypes in Waldenström's macroglobulinemia were IgM κ (19) 70.37%, IgM λ (7) 25.93%. These results are consistent with the results of studies from the Maghreb countries, in which the most common isotypes were the Ig G followed by the Ig A and the IgM in the studies of Mseddi et al in Tunisia, and Belouni et al in Algeria^{11,12}.

Declarations:

Author contribution

All the authors have seen and approved the final manuscript. All authors meet the criteria of authorship

Extracted the clinical and lab data: **KD ,NM ,SB ,SE ,AB ,AR ,AD, AB, AE** ; Acquisition of data: **AE** ; Analysis and interpretation of data: **AE** ; Drafting of manuscript: **AE**; Critical revision:

ZO, AE

Funding

The authors declare no competing financial interests

Conflict of interest

ZO, KD ,NM ,SB ,SE ,AB ,AR ,AD, AB, AE declare that they have no conflict of interest

REFERENCES

1. Mateos MV. How to maintain patients on long-term therapy: understanding the profile and kinetics of adverse events. *Leuk Res* . 2012;36 Suppl 1:S35-43. doi:10.1016/S0145-2126(12)70007-3
2. Hideshima T, Mitsiades C, Tonon G, Richardson PG, Anderson KC. Understanding multiple myeloma pathogenesis in the bone marrow to identify new therapeutic targets. *Nature Reviews Cancer* . 2007;7(8):585-598. doi:10.1038/nrc2189
3. Ogmundsdóttir HM, Haraldsdóttir V, M Jóhannesson G, et al. Monoclonal gammopathy in Iceland: a population-based registry and follow-up. *Br J Haematol* . 2002;118(1):166-173. doi:10.1046/j.1365-2141.2002.03589.x
4. Landgren O, Gridley G, Turesson I, et al. Risk of monoclonal gammopathy of undetermined significance (MGUS) and subsequent multiple myeloma among African American and white veterans in the United States. *Blood* . 2006;107(3):904-906. doi:10.1182/blood-2005-08-3449
5. Landgren O, Katzmman JA, Hsing AW, et al. Prevalence of monoclonal gammopathy of undetermined significance among men in Ghana. *Mayo Clin Proc* . 2007;82(12):1468-1473. doi:10.1016/S0025-6196(11)61089-6
6. Kyle RA, Therneau TM, Rajkumar SV, et al. Prevalence of Monoclonal Gammopathy of Undetermined Significance. *New England Journal of Medicine* . 2006;354(13):1362-1369. doi:10.1056/nejmoa054494
7. Blessum C, Jeppsson JO, Aguzzi F, Bernon H, Bienvenu J. [Capillary electrophoresis: principles and practice in clinical laboratory]. *Ann Biol Clin (Paris)* . 1999;57(6):643-657.
8. Abdallah N, Rajkumar SV, Greipp P, et al. Cytogenetic abnormalities in multiple myeloma: association with disease characteristics and treatment response. *Blood Cancer Journal* 2020 10:8 . 2020;10(8):1-9. doi:10.1038/s41408-020-00348-5
9. Decaux O, Rodon P, Ruelland A, Estepa L, Leblay R, Grosbois B. Épidémiologie descriptive des gammopathies monoclonales. Expérience d'un centre hospitalier général et d'un service de médecine interne de centre hospitalier et universitaire. *Revue de Medecine Interne* . 2007;28(10):670-676. doi:10.1016/j.revmed.2007.04.011
10. Katzmman JA, Kyle RA, Benson J, et al. Screening panels for detection of monoclonal gammopathies. *Clinical Chemistry* . 2009;55(8):1517-1522. doi:10.1373/clinchem.2009.126664
11. Belouni R, Allam I, Cherguelaine K, et al. Epidemiological and immunochemical parameters of monoclonal plasma cell dyscrasias of 2121 cases in Algeria. *Current Research in Translational Medicine* . 2020;68(2):67-70. doi:10.1016/j.retram.2019.11.003
12. Mseddi-Hdiji S, Haddouk S, Ben Ayed M, et al. Gammopathies monoclonales en Tunisie: Analyse épidémiologique, immunochimique et étiologique d'une série de 288 cas. *Pathologie Biologie* . 2005;53(1):19-25. doi:10.1016/j.patbio.2004.01.014
13. R G, M D, L K, et al. Prevalence of Monoclonal Gammopathy of Undetermined Significance in India-A Hospital-based Study. *Clinical lymphoma, myeloma & leukemia* . 2018;18(9):e345-e350. doi:10.1016/J.CLML.2018.06.005
14. Dispenzieri A, Kyle RA, Lacy MQ, et al. POEMS syndrome: definitions and long-term outcome. *Blood* . 2003;101(7):2496-2506. doi:10.1182/blood-2002-07-2299

15. Singh G. Serum and Urine Protein Electrophoresis and Serum-Free Light Chain Assays in the Diagnosis and Monitoring of Monoclonal Gammopathies. *The journal of applied laboratory medicine* . 2020;5(6):1358-1371. doi:10.1093/JALM/JFAA153
16. O L, BI G, JA K, et al. Racial disparities in the prevalence of monoclonal gammopathies: a population-based study of 12,482 persons from the National Health and Nutritional Examination Survey. *Leukemia* . 2014;28(7):1537-1542. doi:10.1038/LEU.2014.34

Hosted file

Tables.docx available at <https://authorea.com/users/517082/articles/591738-epidemiology-of-monoclonal-gammopathy-in-morocco-a-hospital-based-study-running-head-monoclonal-gammopathy>