PREVALENCE OF MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE IN A TERTIARY CARE HOSPITAL OF LAHORE

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ABSTRACT

Background and Objectives: Monoclonal gammopathy of undetermined significance (MGUS) is the most prevalent among the group of disorders called Plasma cell dyscrasias. Differentiating MGUS from other monoclonal gammopathies is important because a conservative management plan is required for individuals with MGUS. Limited research has been done on the epidemiology of MGUS in Pakistan. This study was aimed at estimating the prevalence of MGUS in Pakistani adults.

Methods: A random sample of 383 subjects aged 50 years or older visiting OPD of a tertiary care hospital in Lahore, Pakistan was taken. Individuals having any clinical manifestation of multiple myeloma or related disorders were excluded from the study. Complete blood count (CBC), erythrocyte sedimentation rate (ESR) and Serum Protein Electrophoresis were performed.

Results: The crude prevalence of MGUS was found to be 8.6%, which is higher than observed in previous studies. Multivariate analysis of study subjects showed that old age and elevated ESR were the most important risk factors for MGUS. This is the first research to find out the prevalence of MGUS in the Pakistani adults.

Conclusion: In this study MGUS is seen to be more prevalent in our patients particularly in older age group.

Keywords: Monoclonal gammopathy of undetermined significance, Prevalence, Serum Protein Electrophoresis, Age increment, Erythrocyte sedimentation rate, Anemia.

INTRODUCTION

Monoclonal gammopathy of undetermined significance (MGUS) is a plasma cell disorder,that occurs in 3% of the population aged more than 50 years, and is the commonest among plasma cell dyscrasias.[1,2] The hallmark of Monoclonal gammopathies is the expansion of a single clone of plasma cells, which yields a homogeneous monoclonal protein (M-protein/M-component or paraprotein). MGUS is denoted by less than 3 g/dl M-protein concentration in serum, no or only small amounts of Bence Jones protein in the urine, less than 10% plasma cells in the bone marrow, together with no evidence of lytic bone lesions, anemia, high calcium levels and renal impairment.[3]

MGUS is a known predecessor of malignant hematological disorders, which include multiple myeloma (MM), light chain amyloidosis (AL), and waldenstrom-macroglobulinaemia (WM). However majority of patients with MGUS do not evolve into a plasma cell malignancy.[4] Numerous physical and chemical factors as well as environmental influences have been associated with the origination of MGUS.[5] These include contact with fertilizers, pesticides, mineral oils, asbestos, as well as exposure to radiation.[5] Many cytogenetic and molecular changes observed in MGUS are those that have been seen in multiple myeloma also.[6]

Previous studies have shown that increased patient age increases the prevalence of MGUS and racial variations are also present.[7,8] In the United states, the age-adjusted prevalence of MGUS is three times more in African–Americans as compared to white Americans.[9] Studies from Japan, Taiwan and Thailand show a low prevalence.[10] Sufficient information about the epidemiology of MGUS is limitedin Pakistan. Only a few case reports have been published so far and they were focused on Solitary Plasmacytoma of sternum, Amyloidosis with Multiple Myeloma and lymphoplasmacytic malignancies. We therefore, sought to ascertain the prevalence of MGUS in our adult population.

PATIENTS AND METHODS

A descriptive study was conducted in the Department of Haematology, University of Health Sciences, Lahore from 1st January, 2014 to 31st December, 2014. The informed consent was taken from each participant. After collection of samples from out-patient department of a

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tertiary care hospital in Lahore city, their laboratory analysis was done in the Haematology department, University of Health Sciences, Lahore. Our study included both male and female of age ≥ 50 years and having no clinical evidence of multiple myeloma or related disorders. Persons with age less than 50 years as well as diagnosed cases of multiple myeloma, Primary amyloidosis or waldenstrom macroglogulinemia were excluded from the study. Also excluded were individuals with H/O hypercalcemia, renal insufficiency and lytic bone lesions. Five ml blood was collected using aseptic technique by a trained phlebotomist. It was divided into two vaccutainers, one in EDTA vaccutainer for CBC and ESR, and other for getting the serum to run gel electrophoresis for detection of M-protein band. Electrophoresis was performed by using an agarose gel electrophoresis system Genio S Electrophoresis INTERLAB. After electrophoresis, gels were fixed in acid alcohol, stained and dried. This was followed by identification of protein fractions and sub-fractions.

Statistical Analysis

Statistical analysis was performed using SPSS version 23.0 (IBM Corp, Armonk). Continuous variables were in the form of mean ± standard deviations (SD), whereas categorical variables were in the form of frequency and percentage. Logistic regression analysis was used to estimate the associations between demographic/clinical features and the risk of MGUS. Different risk factors including age, male gender, anemia (hemoglobin < 13 g/dl in males and < 12 g/dl in females) and erythrocyte sedimentation rate > 15 mm/hr were evaluated by univariate as well as multivariate logistic regression analysis. A *p*-value of ≤ 0.05 was considered statistically significant.

RESULTS

Demographic Features of Study subjects:

This study included 383 volunteers. Demographic features of the study subjects have been shown in table 1. Out of the 383 participants, males were 200 (52.2%) and females were 183 (47.8%).The mean age at presentation was 62.78 ± 9.01 years and range was 50–90 years.

Table 1: *Demographic Features of Patients.*

Age	*Male*	*Female*	*Total No*
50 – 60	103	99	202
61 – 70	56	57	113
71 – 80	37	18	55
81 – 90	04	09	13

Prevalence of MGUS

Out of 383 subjects, thirty three patients were found to have MGUS. The crude prevalence of MGUS was found to be 8.6% (Figure 1). Prevalence of MGUS in different age groups and gender wise has been given in table 2. It was observed that the prevalence of MGUS increased with age and was significantly different among age groups ($p<0.05$). Although the prevalence was higher among males (9.5%) than among females (7.7%), but this difference was not statistically significant (p = 0.51).

Table 2: *Prevalence of Monoclonal Gammopathy of Undetermined Significance*

Variables	**Prevalence (95% CI)**
Age	
50 – 60 (n = 202)	4.0% (1.3 – 6.6)
61 – 70 (n = 113)	10.6% (4.9 – 16.3)
71 – 80 (n = 55)	16.4% (6.6 – 26.1)
81 – 90 (n = 13)	30.8% (5.7 – 55.9)
Sex	
Male (n = 200)	9.5%
Female (n = 183)	7.7%
All, crude	8.6% (5.8 – 11.4)

95% CI: 95% Confidence interval

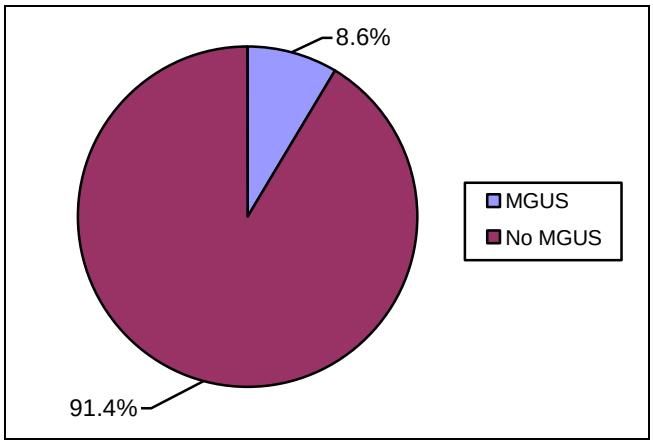

Fig. 1: *Pie chart showing prevalence of MGUS in N = 383 study subjects. Red shows study subjects with MGUS (8.6%) whereas green represents subjects with no MGUS.*

Relation between Risk Factors of MGUS and its prevalence.

Logistic regression analysis was applied to evaluate the association between potential risk factors for MGUS including age, male gender, ESR and anemia. It was found that by applying univariate analysis, prevalence of MGUS increased with age and this was statistically significant (P < 0.001). MGUS was also more prevalent in patients who had increased ESR values (P < 0.001). There was no difference between the MG-

Table 3: *Association between different risk factors and the prevalence of monoclonal gammopathy of undetermined significance*

Variables	*Patients, n (%)*	*Unadjusted OR*	*P value*	*Adjusted OR□*	*P value*
Age (10 – year increase)		2.15 (1.47 – 3.14)	< 0.001	1.62 (1.07 – 2.45)	0.021
ESR > 15 mm/hr	163 (42.6%)	53.49 (7.22 – 396)	< 0.001	43.11 (5.77 – 322)	< 0.001
Anemia	78 (20.4%)	0.70 (0.27 – 1.79)	0.463	‡	‡
Males	200 (52.2%)	1.26 (0.61 – 2.60)	0.520	‡	‡

OR: odds ratio
□ Odds ratio Adjusted by multivariate logistic regression analysis, with 95% CI
ESR: erythrocyte sedimentation rate
†Hb level <13 g/dl in male and <12 g/dl in female
‡Variables excluded after univariate analysis

US group and non-MGUS group (OR = 0.70, 95% CI = 0.27 – 1.79, *P* = 0.463), in relation to anemia. In addition, prevalence of MGUS was not statistically different among gender.

Two risk factors i-e 10-year age increment and increased ESR which were significant in univariate analysis, were then evaluated by multivariate analysis. It was observed that these factors were also found to be significant: age (10-year increase: odds ratio = 1.62, 95% CI = 1.07–2.45, *P* = 0.02), ESR (OR = 43.11, 95% CI = 5.77-322, *P* < 0.001) (Table 3).

DISCUSSION

Monoclonal gammopathy of undetermined significance (MGUS) is a premalignant plasma-cell disorder in which overproduction of immunoglobulins by plasma cells results in hypergammaglobulinemia. MGUS is associated with a rate of progression to multiple myeloma or a related malignant condition of 1 percent per year.[2] Research regarding epidemiology of MGUS is limited in Pakistan. This study was designed to collect the data regarding the prevalence of monoclonal gammopathy, from a tertiary care hospital in Lahore.

In our study population, monoclonal gammopathy was observed in 8.6% of patients. This is comparable to the rate of 7.5% reported in a study carried out in India.[11] However this is higher than the 3.98% reported in Iran.[12] This is also contrary to the lower prevalence rates observed in UK, South America, Eastern Europe, and Japan.[10] So far the biggest and most commonly reported study in whites is that of Olmsted County, Minnesota whose results also differ from our study because the prevalence of MGUS was found to be 3.2% in subjects having age above 50 years and 5.3% in those having age more than 70 years.[13] Blacksdisplayed consistently higher prevalence rates at a given age.[14] Various studies point out towards a geographical variation in the rates of monoclonal gammopathies. This may vary from 5.84% in Ghanaian population[14] to 2.1% in Japan.[15] Although, prevalence observed in our study, is a little higher as compared to previous studies, the reason might be the less population studied as well as racial and environmental variations.

The mean age in our study population was 62.78 ± 9.01 years (range, 50 – 90 years). This is lower in comparison to the previous studies. The mean age as observed by Park et al was 72 years (range: 65 – 97).[8] It was also reported that the increase in age [10 – year increase: odds ratio (OR) = 2.15, *P* < 0.001] was associated with increased prevalence and this is consistent with previous studies.[11,12,15] This rise in prevalence with age was independent of gender or race. In the present study, the prevalence in age group 50 – 60 years was 4% which is similar to that(4.79 %) reported by Afrouzi et al but the prevalence of 10.6 % in age group 61-70 years is higher than the 6.78 % reported in a similar age group by Afrouzi et al.[12] In the group > 80 years of age, we found the prevalence to be 30.8% which is very high as compared to the previously reported 6.7% in the same age group in Korea.[8] This very high result could be due to the fact that in our study population, only 13 individuals fell in this age group whereas the previous study by Park et al in Korea had 75 individuals in this group.[8]

In our study, monoclonal gammopathy was found to be more prevalent in males (9.5%) as compared to females (7.7%) but this difference was statistically not significant. This observation is consistent with previous studies conducted in Iran and Korea.[8,12] Iwanaga et al reported the prevalence as 2.8% males vs1.6 % females.[15] On contrary, Singh et al reported a higher prevalence in women as compared to men in a study done in India.[11]

While evaluating different risk factors, we found that MGUS prevalence was higher in subjects with increased ESR levels (*P* < 0.001). This is consistent with the findings of Park et al.[8] Likewise, similar to the Korean study, no difference was observed when anemia was compared between the study subjects with MGUS and the study subjects with no MGUS.[8] Hence

MGUS was more prevalent with increasing age, male gender and elevated ESR.

Thus, it is obvious that the prevalence of monoclonal gammopathy presented in our study population does not differ significantly from the existing data around the globe. However, it goes without saying that certain nonmalignant diseases may also be associated with monoclonal gammopathy of undetermined significance, for instance Cold agglutinin disease, Acquired von Willebrand syndrome and Membranous nephropathy, and they need to be ruled out.[16] In addition, due consideration must be given to the prospect of overtreatment as well as to stress and anxiety of the patient and economic cost of MGUS follow-up.[17]

Our study had some limitations; study was carried out at a hospital and thus its findings cannot be applicable on whole Pakistani population. Moreover, due to financial constraints, immunofixation was not performed. Further research work is required to verify our findings and to increase the sample population to larger numbers.

It is ***concluded*** that there has been no study regarding the prevalence of MGUS in Pakistani middle aged to old aged persons which is estimated to be 8.6% in our study. There is need of more screening studies of healthy Pakistani population so that we might have convincing data about the prevalence of MGUS in our country. The authors also recommend further research plans to follow-up MGUS patients to describe the mechanism for cancer development.

Authors' Contribution

JA: Data collection, Analysis and interpretation of data. NM: Literature review, Manuscript writing, Data analysis. AH: Manuscript writing, Statistical analysis, Critical revision of article GMC: Data collection and lab work SM: Concept and design, Final approval and guarantor of the article.

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Conflict of Interest

None declared.

REFERENCES

1. McShane CM, Murphy B, Lim KH, Anderson LA. Monoclonal gammopathy of undetermined significance as viewed by haematology healthcare professionals. J. Europ Haem. 2018; 100 (1): 20-6.
2. Turesson I, Kovalchik SA, Pfeiffer RM, Kristinsson SY, Goldin LR, Drayson MT, et al. Monoclonal gammopathy of undetermined significance and risk of lymphoid and myeloid malignancies: 728 cases followed up to 30 years in Sweden. Blood, 2014; 123 (3): 338-45.
3. van de Donk NW, Palumbo A, Johnsen HE, Engelhardt M, Gay F, Gregersen H, et al. The clinical relevance and management of monoclonal gammopathy of undetermined significance and related disorders: recommendations from the European Myeloma Network. Haematologica. 2014; 99 (6): 984-96.
4. Glavey SV, Leung N. Monoclonal gammopathy: the good, the bad and the ugly. Blood Reviews, 2016; 30 (3): 223-31.
5. Wadhera RK, Rajkumar SV. Prevalence of monoclonal gammopathy of undetermined significance: a systematic review. Mayo Clinic Proceedings, 2010; 85 (10): 933-942.
6. Schmidt-Hieber M, Gutiérrez ML, Pérez-Andrés M, Paiva B, Rasillo A, Tabernero MD, et al. Cytogenetic profiles in multiple myeloma and monoclonal gammopathy of undetermined significance: a study in highly purified aberrant plasma cells. Haematologica. 2013; 98 (2): 279-87.
7. Mangiacavalli S, Cocito F, Pochintesta L, Pascutto C, Ferretti V, Varettoni M, et al. Monoclonal gammopathy of undetermined significance: a new proposal of workup. J Europ Haemat. 2013; 91 (4): 356-60.
8. Park HK, Lee KR, Kim YJ, Cho HI, Eun Kim J, Woong Kim K, et al. Prevalence of monoclonal gammopathy of undetermined significance in an elderly urban Korean population. J Am Hemat. 2011; 86 (9): 752-5.
9. Go RS, Gundrum JD, Neuner JM. Determining the Clinical Significance of Monoclonal Gammopathy of Undetermined Significance: A SEER–Medicare Population Analysis. Clin Lymph, Myelo & Leuk. 2015; 15 (3): 177-86.
10. Agarwal A, Ghobrial IM. Monoclonal gammopathy of undetermined significance and smoldering multiple myeloma: a review of the current understanding of epidemiology, biology, risk stratification, and management of myeloma precursor disease. Clinical Cancer Research, 2012; 19 (5): 985–994.
11. Singh K, Singh B, Arora S, Saxena A. Immunological evidence of monoclonal gammopathy in north India: a hospital based study. Path & Lab Medi Int. 2010; 2: 107-111.
12. Afrouzi M, Aghili B, Gholamrezaei M, Adel M, Matin Z. Monoclonal Gammopathy in Iran: Prevalence and Isotype Distribution. MOJ Immunol. 2014; 1 (5): 1-3.
13. Kyle R, Durie B, Rajkumar SV, Landgren O, Bladé J, Merlini G, et al. Monoclonal gammopathy of undetermined significance (MGUS) and smoldering (asymptomatic) multiple myeloma: IMWG consensus perspectives risk factors for progression and guidelines for monitoring and management. Leukemia, 2010; 24 (6): 1121-1127.
14. Landgren O, Graubard B, Kumar S, Kyle R, Katzmann J,

Murata K, et al. Prevalence of myeloma precursor state monoclonal gammopathy of undetermined significance in 12372 individuals 10–49 years old: a population-based study from the National Health and Nutrition Examination Survey. J Blood Canc. 2017; 7 (10): e618.

15. Iwanaga M, Tomonaga M. Prevalence of monoclonal gammopathy of undetermined significance in Asia: a viewpoint from nagasaki atomic bomb survivors. Clinical Lymphoma, Myeloma and Leukemia, 2014 Feb. 1; 14 (1): 18-20.
16. Go RS, Rajkumar SV. How I manage monoclonal gammopathy of undetermined significance. Blood, 2018; 31 (2): 163-173.
17. Go RS, Swanson KM, Sangaralingham LR, Habermann EB, Shah ND. Clinical prevalence (diagnosed cases) of monoclonal gammopathy of undetermined significance in the US: estimating the burden on health care. Leukemia. 2016; 30 (6): 1443-1446.