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Clinical Manifestations, Immunoglobulin Subtypes, and Chromosomal Translocations in Multiple Myeloma: A Tertiary Care Center Study from Pakistan

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ABSTRACT

Objective: To analyze the clinical manifestations, immunoglobulin subtypes, and chromosomal translocations in multiple myeloma patients at a tertiary care center in Rawalpindi, Pakistan.

Study Design: Retrospective descriptive study

Place and Duration of Study: Department of Immunology, Armed Forces Institute of Pathology, NUMS, Rawalpindi, Pakistan, from Aug 2021 to Aug 2024.

Methodology: In this study, 100 symptomatic patients of multiple myeloma were included. Serum protein electrophoresis was performed to detect abnormal paraproteins produced by myeloma cells, followed by Immunofixation electrophoresis to characterize the type of abnormal paraproteins. Fluorescence in situ hybridization was used to detect chromosomal translocations and other genetic abnormalities in 38 patients. Chi-square test was applied to find any significant association between identified translocations and clinical features. A p-value less than 0.05 was deemed statistically significant.

Results: Out of 100 cases, the majority of participants were male (64.0%) with ages ranging from 38 – 82 years. Chromosomal analysis by FISH revealed that most frequent translocations were t(4;14) in 5(13.2%) patients, t(11;14) in 4(10.5%), and t(14;18) in 3(7.9%) patients. A co-occurrence of t(4;14), del(1p32), and gain(1q21) was observed in 3(7.9%) patients. Regarding immunoglobulin isotypes, IgG was present in 66 patients (65.0%), IgA was present in 27.0% of cases, while light chain myeloma was found in 6% of cases.

Conclusions: Multiple myeloma is a complex hematologic malignancy requiring comprehensive evaluation of clinical presentations, immunoglobulin subtypes, and genetic abnormalities for effective patient management. Continued research is crucial for enhancing therapeutic strategies and improving the quality of life for affected patients.

Keywords: Cytogenetic profiles, Multiple Myeloma, Plasma cell neoplasms

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INTRODUCTION

Multiple myeloma is the second most common hematological malignancy and accounts for almost 15 - 17 % of blood cancers and approximately 1-2% of all malignancies.[1,2] It originates from abnormal plasma cells in the bone marrow & poses distinct challenges in diagnosis. It is a disease of older adults and slightly more frequent in males than females. Heterogeneity of clinical symptoms, immunoglobulin subtypes, and molecular patterns requires a multimodal approach for accurate diagnosis and a better treatment strategy.[3] The clinical presentation of multiple myeloma is often subtle and diverse, making it a diagnostic puzzle. Multiple myeloma often presents with symptoms arising due to infiltration of malignant plasma cells into the bone, other organs, or due to renal damage from immunoglobulin deposition.[4] Understanding and recognizing these heterogeneous clinical manifestations are pivotal for timely diagnosis and initiation of appropriate treatment necessary for the diagnosis of multiple myeloma.[5,6]

One of the distinctive features of multiple myeloma lies in the aberrant production of monoclonal immunoglobulins, or M proteins, by malignant plasma cells. Immunoglobulin subtypes, such as IgG, IgM, IgA, IgE, and IgD, can be identified through sophisticated laboratory techniques like serum protein electrophoresis (SPEP) and immunofixation electrophoresis (IFE) and serum FLC assay. The detection of these abnormal proteins not only aids in confirming the diagnosis but also serves as a valuable tool for disease monitoring and risk stratification.[1,7] Advancements in genetic testing have significantly enhanced the understanding of critical genetic abnormalities associated with the disease. Identifying specific chromosomal translocations and

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genetic mutations has become essential for refining diagnosis and guiding personalized treatment strategies.[8]

This study was conducted to gain better insights regarding clinical manifestations, immunological subtypes, and chromosomal translocations in multiple myeloma patients within the Pakistani population. Due to ethnic and regional variations, consideration of these factors is crucial for accurate diagnosis and management. These findings will contribute to improving risk stratification and personalized treatment strategies in local clinical practice.

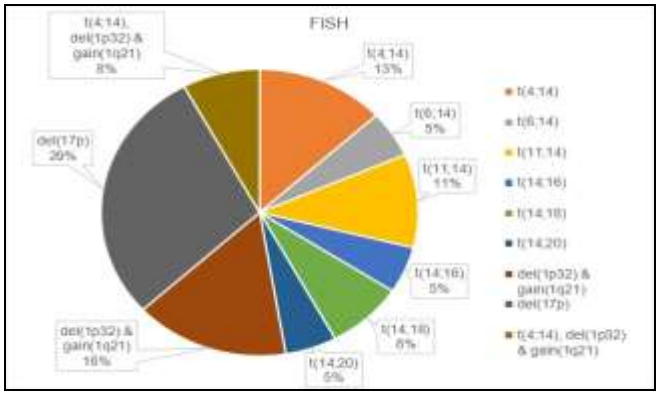

Figure-1: Distribution of Genetic Abnormalities Detected by Fluorescence In Situ Hybridization (n= 38)

METHODOLOGY

This retrospective descriptive study was conducted at the Immunology Department, Armed Forces Institute of Pathology, Rawalpindi, Pakistan, from Aug 2021 to Aug 2024 after the approval of the Institutional Review Board (IRB no: IRB/20/3712). Sample size (n) was calculated using the OpenEpi sample size calculator (online) by keeping the prevalence of multiple myeloma in suspected cases 6.88%, confidence level 95%, and margin of error ± 5%. An adequate sample size came out to be 99; however, 100 patients were included in this study.[9,10] Non-probability consecutive sampling technique was used; consent was taken from all the participants, and strict confidentiality was maintained throughout the study process.

The data was collected using a questionnaire specifically designed to document demographic information and laboratory findings of the patients. Inclusion criteria: patients of either gender with no age limitations who were diagnosed with cases of multiple myeloma before receiving any treatment were included in this study. Exclusion criteria: patients with a concurrent or recent history of other cancers, and patients who have received specific prior treatments were excluded to avoid confounding variables that could impact the interpretation of results. After documentation of detailed demographic and clinical features of the patients, blood samples were drawn for serological and molecular analysis. SPEP was performed to detect paraproteins produced by myeloma cells, followed by IFE to characterize the type of abnormal proteins present.

Data were analyzed using the Statistical Package for the Social Sciences (Version 26, IBM Corp; Armonk, USA). Quantitative variables are presented as mean and standard deviation, while qualitative variables are expressed as frequencies and percentages. The association between clinical manifestations of multiple myeloma and specific chromosomal translocations was analyzed using Fisher's exact test. A p-value ≤ 0.05 was considered statistically significant.

RESULTS

Of the total 100 patients of Multiple Myeloma, there were 64(64%) males and 36(36%) females (M: F = 1.7:1) with a mean age of 59.9±12.9 years, ranging from 38 to 82 years. Concerning the immunoglobulin (Ig) isotype distribution in patients with multiple myeloma, IgG accounted for 66% of cases, IgA for 27%, and only light chain myeloma for 6%. IgM myeloma was the least common subtype (1%), and there were no IgD and IgE phenotypes identified. In terms of clinical features, anemia was the most prevalent symptom, affecting 78% of the participants, followed by bone pain, which was reported in 73% of cases. Hypercalcemia was observed in 54% of individuals, while renal insufficiency affected 39%. Fatigue was reported by 70% of participants, and 38% had experienced infections during the course of their illness. Demographics, clinical characteristics, and SPE-IFE findings are presented in Table I.Fluorescence In Situ Hybridization (FISH) was performed to determine the underlying chromosomal abnormalities in 38 patients only. Figure-1 shows the distribution of different genetic abnormalities in those patients, with del(17p) being the most frequent anomaly detected in 11(29%) patients, followed by del(1p32) and gain(1q21) mutation in 6 (16%) patients. Similarly, t(4;14) was found in 5(13%) patients and a combination of t(4;14), del(1p32) & gain(1q21) in 3 (8%) of the cases. t(11;14) and t(14;18) were found in 4 (11%) and 3 (8%) patients, respectively. Meanwhile, t(14;20), t(6;14), and t(14;16)

each accounted for 2(5%) each, of the 38 MM patients (Figure 1). Distribution of chromosomal translocations along with respective clinical features and Immunoglobulin (Ig) isotype are presented in Table II. As presented in Table-II, Fisher's exact test was used to determine the association between disease characteristics and primary cytogenetic abnormalities. The analysis revealed no statistically significant association between the type of immunoglobulin (SPE-IFE) and the genetic mutations (p = 0.559). Similarly, clinical features such as hypercalcemia (serum calcium >2.75 mmol/L) (p = 0.141), renal insufficiency (serum creatinine >177mol/L) (p = 0.922), anemia (Hemoglobin <10g/dL) (p = 0.193), bone pain (p = 0.824), infection (p = 0.650) and fatigue (p = 0.766) did not show statistically significant association with the genetic defects, implying that these conditions are more evenly distributed across the different genetic profiles.

Table-I: Demographics, clinical features, and Serum Protein Electrophoresis–Immunofixation Electrophoresis findings (n=100)

Parameter		Percentage
Gender	Male	64%
	Female	36%
SPE-IFE		
IgG κ		47 %
IgG λ		19 %
IgA κ		16 %
IgA λ		11 %
IgM Myeloma		1 %
LCMM		6 %
Clinical Features		
Hypercalcemia (serum calcium >2.75 mmol/L)		54 %
Renal insufficiency (serum creatinine >177mol/L)		39 %
Anemia (Hemoglobin <10g/dL)		78 %
Bone pain		73 %
Infection		38 %
Fatigue		70%

**SPE-IE - Serum Protein Electrophoresis–Immunofixation Electrophoresis, IgG κ - Immunoglobulin G kappa, IgG λ- Immunoglobulin G lambda, IgA κ - Immunoglobulin A kappa, IgM – Immunoglobulin M, LCMM – Latent Class Mixed Models, mmol/L – millimole per litre, g/dL – gram per decilitre,*

DISCUSSION

In this study, FISH was used to identify chromosomal abnormalities in 38 patients with multiple myeloma. Although this is a single-centre study, these findings provide valuable insights into the genetic landscape of this hematological malignancy in the local population. The most frequent abnormality detected was del (17p), present in 11 (29%) patients, followed by del (1p32) and gain (1q21), each occurring in 6(16%) patients. Other abnormalities included t(11;14) (11%) and t(14;18) (8%). Whereas t(14;20), t(6;14), and t(14;16) were detected in 2 (5%) patients each.

Multiple myeloma arises from malignant plasma cells and is characterized by diverse manifestations, intricate immunoglobulin subtypes, and distinctive molecular patterns. A deeper understanding of these aspects is essential for precise diagnosis, treatment decisions, and continued progress in research.[10] The clinical manifestations of multiple myeloma are broad and often insidious, making early detection a challenge. One of the commonest presenting symptoms of this disease is bone pain due to the disease's predilection for bone marrow and skeletal structures and infiltration of plasma cells. Other symptoms include fatigue, weight loss, anemia, and recurrent infections, contributing to the heterogeneity of clinical presentations in this condition.[11] Moreover, bone marrow function is compromised due to infiltration of malignant plasma cells, leading to cytopenias, which contribute to the anemia, increased susceptibility to infections, and bleeding complications.[12] These malignant plasma cells lead to the production of monoclonal immunoglobulins, known as M proteins, or paraproteins. Immunological characterization of these abnormal monoclonal proteins, including immunoglobulin subtypes, IgG, IgA, IgM, IgD, and IgE, is pivotal in the diagnosis of this condition.[13]

For identification and characterisation of M proteins, serum protein electrophoresis and immunofixation electrophoresis are performed. The identification of Bence Jones proteins in the urine and measurement of serum free light chains further add to diagnosis. It is important to highlight that identification of these immunoglobulin subtypes is not only important for diagnosis but also of prognostic significance. This variability in immunoglobulin subtypes needs precise diagnostic approaches to correctly diagnose multiple myeloma patients. [14] It is pertinent to mention that genetic abnormalities are one of the key prognostic factors in these patients. Identification of genetic mutations is required for risk stratification, as recommended in the revised international staging system (R-ISS), established by the International Myeloma Working Group.[15] Besides their prognostic significance, mutation analysis is also important to customize therapeutic strategies for offering more individualized treatment to the patients,

Table II: Distribution Of Chromosomal Translocations Along With Respective Clinical Features And Immunoglobulin (Ig) Isotype

Parameters		All	t(4;14) (13.15 %)	t(6;14) (5.2 %)	t(11;14) (10.4 %)	t(14;16) (5.2 %)	t(14;20) (5.2 %)	del(1p32) with gain(1q21) (15.7 %)	del(17p) (28.9 %)	t(4;14), del(1p32), and gain(1q21) (7.8 %)	t(14;18) (7.8 %)	*p*-value
No. of Subjects		n=38	n=5	n=2	n=4	n=2	n=2	n=6	n=11	n=3	n=3	
Gender	Male	26 (68.4%)	3 (60.0%)	2 (100.0%)	4 (100.0%)	1 (50.0%)	0 (0.0%)	4 (66.7%)	7 (63.6%)	2 (66.7%)	3 (100.0%)	0.418
	Female	12 (31.6%)	2 (40.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)	2 (100.0%)	2 (33.3%)	4 (36.4%)	1 (33.3%)	0 (0%)	
Serum Protein Electrophoresis–Immunofixation Electrophoresis												
IgG κ		15 (39.0%)	0 (0.0%)	2 (100.0%)	0 (0.0%)	1 (50.0%)	2 (100.0%)	3 (50.0%)	3 (27.3%)	2 (66.7%)	2 (66.7%)	0.559
IgG λ		5 (13.0%)	1 (20.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)	0 (0.0%)	1 (16.6%)	2 (18.2%)	0 (0.0%)	0 (0.0%)	
IgA κ		8 (21.0%)	3 (60.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (16.6%)	3 (27.3%)	1 (33.3%)	0 (0.0%)	
IgA λ		3 (8.0%)	1 (20.0%)	0 (0.0%)	1 (25.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.0%)	0 (0.0%)	0 (0.0%)	
IgM Myeloma		1 (3.0%)	0 (0.0%)	0 (0.0%)	1 (25.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
LCMM		6 (16.0%)	0 (0.0%)	0 (0.0%)	2 (50.0%)	0 (0.0%)	0 (0.0%)	1 (16.6%)	2 (18.2%)	0 (0.0%)	1 (33.3%)	
Clinical features												
Hypercalcemia		15 (39.5%)	2 (40.0%)	2 (100.0%)	2 (50.0%)	0 (0.0%)	2 (100.0%)	0 (0%)	5 (45.4%)	1 (33.3%)	1 (33.3%)	0.141
Renal insufficiency		21(55.2%)	3 (60.0%)	1 (50.0%)	2 (50.0%)	1(50.0%)	0 (0.0%)	4 (66.6%)	7 (63.6%)	2 (66.7%)	1 (33.3%)	0.922
Anemia		27 (71.1%)	4 (80.0%)	1 (50.0%)	2 (50.0%)	1 (50.0%)	0 (0.0%)	6 (100.0%)	8 (72.7%)	2 (66.7%)	3(100.0%)	0.193
Bone pain		32 (84.2%)	4 (80.0%)	1 (50.0%)	4(100.0%)	2 (0.0%)	2 (100.0%)	4 (66.6%)	9 (81.8%)	3 (100.0%)	3 (100.0%)	0.824
Infection		24 (63.2%)	4 (80.0%)	1 (50.0%)	4 (100.0%)	1 (50.0%)	2 (100.0%)	3 (50.0%)	6 (54.5%)	1 (33.3%)	2 (66.7%)	0.650
Fatigue		29 (76.3%)	5 (100.0%)	2(100.0%)	3 (75.0%)	1 (50.0%)	2 (100.0%)	4 (66.6%)	7 (63.6%)	2 (66.7%)	3 (100.0%)	0.766

** IgG κ - Immunoglobulin G kappa, IgG λ- Immunoglobulin G lambda, IgA κ - Immunoglobulin A kappa, IgM – Immunoglobulin M, LCMM - Latent Class Mixed Models, t = Translocation, del – deletion, gain – chromosomal gain, 1p – short arm chromosome, 1q – long arm chromosome*

to enhance treatment efficacy and improve patient outcomes as reported by Orzetti *et al*.[16] For genetic analysis in these patients, advanced molecular techniques play a pivotal role, and the main techniques employed for this purpose include FISH, single nucleotide polymorphism analysis, and next-generation sequencing, which were recommended in the literature by Cardona *et al*.[17] The study of possible genetic anomalies, including chromosomal translocations, copy number abnormalities, and point mutations, provides valuable insights into the molecular pathology of multiple myeloma for a better understanding of this disease.

These results highlight the variability of multiple myeloma, with del(17p) being identified as the most common mutation, a recognized high-risk genetic marker in the Revised International Staging System (R-ISS), which was also reported in a study by Hagen *et al*.[18] It is important to highlight that translocations like t(4;14) and t(14;16) are classified as high-risk factors, leading to poorer outcomes and requiring customized treatment approaches. In a study by Zaheer *et al*., FISH analysis for t(4;14) was positive in 15% of patients and negative in 85% of patients. Those with a positive result showed significantly impaired renal function and higher beta-2 microglobulin levels compared to patients without the translocation.[19] In contrast, t (11;14), often regarded as a standard-risk, is linked to a slower disease progression and responds favorably to treatments such as Lenalidomide.[20] In a study by Hussain *et al*., clinicopathological features of multiple myeloma in the Pakistani population were reported; however, FISH and cytogenetic analyses were not performed. Bone pain was the most common symptom reported in 33(50.8%) patients, followed by backache in 32(49.2%) patients.[21] Risk stratification using the international staging system classified 20(30.7%) patients in stage I, 19(29.1%) in stage II, and 26(40.2%) in stage III.[22]

Findings of this study highlight the importance of cytogenetic studies in the management of multiple myeloma. Additionally, findings of this study revealed that genetic variations did not notably influence clinical symptoms like hypercalcemia, renal failure, anemia, bone pain, infections, and fatigue, and clinical features were uniformly distributed among different multiple myeloma patients, irrespective of their genetic anomalies.

LIMITATION OF STUDY

This was a single-center study, and the findings may not apply to other demographics. Furthermore, resource limitations restricted the use of FISH testing to only 38 cases,

limiting the possibility to analyze chromosomal translocations in a wider study population. Given these limitations, future multicenter studies with larger cohorts are required for generalizability of findings of this study. Comprehensive assessment of clinical features, laboratory findings, and radiological studies is important in the timely and accurate diagnosis of multiple myeloma patients. Furthermore, identifying specific genetic mutations has become essential for tailoring treatment approaches for better prognosis in multiple myeloma.

CONCLUSION

The variation in clinical manifestations, immunoglobulin subtypes, and associated genetic mutations highlights the complexity in diagnostic evaluation of this hematological malignancy. Multi-centre studies with larger patient cohorts may expand comprehension of this condition within the local population, leading to better therapeutic strategies to reduce morbidity and mortality.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

MA & HNT: Data acquisition, data analysis, critical review, approval of the final version to be published.

MAH & MH: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

MZUA: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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