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Clinicobiochemical profile in *de novo* multiple myeloma: A study from North India

Mir Sadaqat Hassan Zafar[1], Raiesa[2], Maqsood Ahmad Dar[3], Manzoor Ahmad Sofi[4]

[1]Consultant, [4]Senior Resident, Department of Clinical Hematology, Superspeciality Hospital, [2]Postgraduate Scholar, Department of Microbiology, [3]Consultant, Department of Medicine, Government Medical College, Srinagar, Jammu and Kashmir, India

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ABSTRACT

Background: Multiple myeloma (MM) is the second most common hematological malignancy after non-Hodgkin lymphoma. The clinical spectrum varies from asymptomatic forms to manifestations of anemia, bone pains, and eventually spontaneous fractures, renal failure, and frequent infections. **Aims and Objectives:** The aims and objectives of the study are to assess the clinical and biochemical parameters in newly diagnosed cases of MM. **Materials and Methods:** This study was conducted in the Department of Clinical Hematology of a tertiary care hospital of North India. It was a prospective observational study over a period of 2-year duration. A total of 50 newly diagnosed patients of MM were enrolled and analyzed for clinical data. **Results:** Out of 50 MM patients, 68% were males and 32% were females. Mean ± SD of age was 62.48 ± 8.140 years. Forty patients (80%) had anemia (isolated anemia 4 patients), 22 patients had renal failure (44%), 20 patients (40%) had spontaneous fractures (isolated pathological fracture 6 patients), and 14 patients (28%) had bone pains (isolated bone pains 4 patients). Mean ± SD of hemoglobin before the start of treatment was 8.69 ± 2.85 g/dL. Twenty-six patients (52%) had associated comorbidity mainly hypertension (32%) and diabetes mellitus (8%), while 48% of patients had no history of previous comorbid illness. Immunoglobulin (Ig)G-λ type MM were 16 cases (32%), IgA-λ type were 6 cases (12%), IgG-κ were 10 cases (20%), IgA- κ were 4 cases (8%), Kappa type were 10 cases (20%), and biclonal 2 cases (4%). Twelve patients (24%) were in the International Staging System (ISS), 22 patients (44%) in ISS-II, and 16 patients (32%) in ISS-III disease stage. **Conclusion:** Treating physician should have a high index of suspicion for this disorder once elderly patients present with anemia, especially in combination with renal dysfunction and/spontaneous fractures for early diagnosis and treatment.

Key words: Multiple myeloma; Anemia; Renal dysfunction; Bony pains

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INTRODUCTION

Multiple myeloma (MM) arises commonly from a monoclonal gammopathy of undetermined significance (MGUS) that progresses to smoldering MM (SMM) and finally to active or symptomatic MM.[1] Thus, MM shows a clinical spectrum that varies from asymptomatic forms to manifestations of anemia, bone pains, and finally spontaneous fractures, renal failure, or frequent infections.[2]

MM is the second most common hematological cancer after non-Hodgkin lymphoma. It comprises about 1% of malignant neoplasms, 10–15% of hematopoietic tumors and causes, and 20% of deaths from hematological malignancies. Overall survival ranges from few months to more than 10 years (median 3–5 years).[3]

The overall outcome of patients with MM treated with conventional chemotherapy with or without high-dose therapy/autologous stem cell transplantation has not been satisfactory, with median survivals ranging from 2 to 3 years for older patients (>65 years) and from 5 to 6 years for younger patients (<65 years).[4] Although MM remains incurable, outcomes have improved substantially over recent

Address for Correspondence:
Dr. Mir Sadaqat Hassan Zafar, Consultant, Department of Clinical Hematology, Superspeciality Hospital, Srinagar, Jammu and Kashmir, India. **Mobile:** +91-7006153304. **E-mail:** mir.sadaqat@gmail.com

years as a result of the availability of newer agents such as immunomodulatory drugs (thalidomide and lenalidomide) and proteasome inhibitor (bortezomib and carfilzomib) with novel mechanisms of action. Following the introduction of these drugs in the relapsed or refractory setting, they have also been included in the frontline treatment of MM. Recent efforts have focused on improving response rates and in particular complete response rates by including these agents in induction regimens.[5]

Different chromosomal abnormalities have been proven to play an important prognostic role in the outcome of MM. For example, del (13), t (4;14), del (17p), and t (14;16) displayed a specific poor outcome whereas hyperdiploidy and t (11;14) translocation are associated with better outcomes. Bortezomib and carfilzomib appear to be effective in patients with cytogenetic abnormalities.[6]

With this background, the present study was conducted in the Department of Clinical Hematology of a tertiary care teaching hospital from north India. The main aim of this study was to analyze the clinical and biochemical parameters of newly diagnosed cases of MM to form a baseline hospital data for future reference.

Aims and objectives

The main aim of this study was to analyze the clinical and laboratory profile in newly diagnosed patients of MM and subsequently mark the factors with high index of suspicion for its diagnosis and early treatment. Furthermore, this will form the baseline data for future referencing from a tertiary care hospital.

MATERIALS AND METHODS

This study was conducted in the Department of Clinical Hematology of a tertiary care hospital of North India. It was a prospective observational study for 2-year duration. A total of 50 newly diagnosed patients of MM were enrolled after taking an informed consent.

Inclusion criteria

Newly diagnosed cases and previously untreated patients whose age was more than 18 years with symptomatic disease were included in the study.

Exclusion criteria

Patients with, relapse or refractory disease, associated with another cancer, grade 2–4 peripheral neuropathy before the start of treatment, asymptomatic myeloma, or uncontrolled cardiovascular disease (NYHA class 3–4) were excluded from the study.

Demographic data, detailed medical history, physical examination including clinical assessment of neuropathy, and all the baseline investigations (complete blood count, ESR, kidney function tests, liver function tests, serum and urine protein electrophoresis, serum and urine immunofixation studies, bone marrow aspiration/biopsy, β_2 microglobulin, lactate dehydrogenase (LDH), uric acid, random blood glucose, and serum calcium levels) were analyzed for each patient. Cytogenetics and interphase FISH studies were performed only in few patients due to affordability issues and non-availability in our institute. The international myeloma working group criteria were used for diagnosis and the international staging system (ISS) was used for disease staging.

Statistical analysis

The data in each case were collected based on the pro forma attached. Descriptive statistics were used for data analysis. Continuous variables are presented as mean±SD. Categorical variables are expressed as frequencies and percentages. SPSS-17 for Windows statistics package (Microsoft Corp., Richmond, VA) was used for the analysis.

RESULTS

A total of 50 newly diagnosed patients of MM were taken after proper diagnosis and before the start of treatment. Out of these, 68% were males and 32% were females with all the patients >50 years of age. Forty patients (80%) had anemia out of which isolated anemia was seen in 4 (8%) patients at presentation, 22 patients (44%) had renal failure, 14 (28%) patients had spontaneous fractures out of which isolated pathological fracture was seen in 12% cases and 20 (40) patients had bone pains out of which isolated bone pains were seen in 8% cases. Anemia was seen as the most common presenting feature followed by renal failure and spontaneous fractures (Table 1).

Baseline mean±SD of hemoglobin of 50 patients before the start of treatment was 8.69±2.85 g/dL. Baseline mean±SD of serum creatinine of 50 patients was 2.02±3.36 mg/dL. Baseline mean±SD of glucose, calcium, uric acid, LDH, β2 microglobulin, and albumin were 108.44±14.33 mg/dL, 9.42±1.22 mg/dL, 6.20±3.34 mg/dL, 222.24±68.44 IU/L, and 4.02±3.22 mg/L, respectively.

Out of 50 patients of MM, 26 patients (52%) had associated comorbidity mainly hypertension (32%) and

Table 1: Frequency of main presenting features (n=50)

Presenting feature	Frequency (%)
Anemia	40/50 (80)
Bone pains	20/50 (40)
Pathologic fracture	14/50 (28)
Renal failure	22/50 (44)

diabetes mellitus (8%), while 48% of patients had no history of previous comorbid illness (Table 2).

On immunofixation electrophoresis, immunoglobulin (Ig) G-λ type MM were 16 cases (32%), IgA-λ type were 6 cases (12%), IgG-κ were 10 cases (20%), IgA- κ were 4 cases (8%), Kappa type were 10 cases (20%), and biclonal 2 cases (4%) (Table 3).

Of 50 patients, 12 patients (24%) were in ISS-I, 22 patients (44%) in ISS-II, and 16 patients (32%) in ISS-III disease stage (Table 4).

DISCUSSION

MM at presentation needs urgent clinical assessment for various myeloma-related complications to prevent further progression and by managing the emergency issues such as fractures and cord compression. The osteolytic bone lesions in MM exhibit no new bone formation unlike other malignancies that infiltrate bone. Routine skeletal radiographs, magnetic resonance imaging, or fluorodeoxyglucose positron emission tomography/computed tomographic scans are used to detect the bone disease.[7] Anemia, hypercalcemia, renal failure, and an increased risk of infections form other major clinical manifestations. Extramedullary disease (EMD) occurs in approximately 1–2% of patients at the time of initial diagnosis, while as 8% cases develop EMD later on in the disease course.[8] Almost every patient with MM evolves from an asymptomatic pre-malignant stage termed MGUS.[9,10] The rate of progression or transformation is affected by the underlying cytogenetics of disease. Patients with t (4; 14) translocation, 17p deletion, and 1q amplification appear to be at a higher risk of progression from SMM to MM.[11,12]

Table 2: Distribution of comorbidities (n=50)

Co-morbidity	Frequency (%)
Not present	24 (48)
HTN	16 (32)
DM	4 (8)
DM+HTN	4 (8)
Asthma+CAD	2 (4)
Total	50 (100)

HTN: Hypertension, DM: diabetes mellitus, CAD: Coronary artery disease

Table 3: Type of multiple myeloma by immunofixation (n=50)

Type of MM	n
IgG-λ	16
IgA-λ	8
IgG κ	10
IgA-κ	4
Light chain κ	10
Biclonal bands-IgG λ and λ light chain	2

MM: Multiple myeloma, Ig: Immunoglobulin

Table 4: International staging system (n=50)

Stage	Frequency (%)
ISS-I	12/50 (24)
ISS-II	22/50 (44)
ISS-III	16/50 (32)

ISS: International staging system

Diwan et al. (2014) documented that the sixth decade is the common age group with a mean of 62 years. Kyle and Rajkumar (2003) documented that the mean age was 66 years with 2% younger than 40 and 38% older than 70 years. Kumar et al. (2006) from India reported that the median age is 55 years. Kumar et al. documented male: female ratio 1.5:1.[13,14] Our study population comprised of 34 males and 16 females (50–80 years) with M: F ratio of 2.1:1. Bone pain was documented by Madhu et al., in 78.1% and Diwan et al., in 85% of patients. Our study showed bone pains in 40% of patients.

Barlogie et al. showed mean hemoglobin level >8.5 g/dL and Diwan AG et al. found anemia in 100%, and Rahman et al. found mean hemoglobin of 7.56. Anemia was seen in 80% of patients in our study (mean±SD [hemoglobin]: 9.19±3.05 [g/dL]), renal failure in 44% of patients, spontaneous fractures in 28% of patients, and bone pains in 40% of patients.[15]

Fifty-two percent of patients had comorbid illness including hypertension (32%), hypertension plus diabetes mellitus (8%), diabetes mellitus (8%), and coronary artery disease (4%). All the patients were receiving treatment for comorbid illnesses throughout the study. Hypercalcemia was seen in 16% of patients and hyperuricemia in 40% of patients at presentation, both of these disorders improved with proper hydration, and specific treatment besides the introduction of bortezomib plus dexamethasone.

IgG-λ type MM was seen in 16 patients (32%), IgG-κ type in 10 patients (20%), light chain myeloma in 10 (κ light chain) patients (20%), IgA-λ type in 8 patients (16%), IgA-κ type in 4 patients (8%), and 2 patients (4%) had biclonal myeloma. Out of 50 patients, 12 patients (24%) were in ISS-I, 22 patients (44%) in ISS-II, and 16 patients (32%) in ISS-III disease stage. Recent reports show approximately 30% of patients with diagnosed MM present with baseline renal dysfunction. Renal failure has been associated with shorter survival or early patient mortality. Madhu et al., Diwan et al., Kumar et al., and Blade et al. showed serum creatinine level >2 mg/dL in 13.8%, 30%; 31.3%, and 22.3%, respectively.[14]

Limitations of the study

The limitation of present study was smaller sample size which can be improved by a future prospective study with larger number of cases.

CONCLUSION

Anemia is the most common presenting feature followed by bony pains, renal failure, and pathological fractures in newly diagnosed cases of MM. This study highlights the significance of high index of suspicion for this disorder once elderly patients present with anemia, especially in combination with renal dysfunction and spontaneous fractures, leading to early diagnosis and quick treatment. The biochemical parameters such as serum creatinine, calcium, protein electrophoresis, immunofixation, and free light chains assay form important diagnostic panel with the bone marrow examination.

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Authors' Contributions:
MSHZ- Definition of intellectual content, implementation of study protocol, data collection, data analysis, manuscript preparation, article submission, and article revision; **R-** Data analysis, literature survey, manuscript preparation, manuscript editing, and manuscript revision; **MAD-** Review manuscript; **MAS-** Coordination and review.

Work attributed to:
Department of Clinical Hematology, Superspeciality Hospital, Srinagar, Jammu and Kashmir, India.

Orcid ID:
Raiesa - https://orcid.org/0009-0000-7575-9431
Maqsood Ahmad Dar - https://orcid.org/0000-0003-2143-8071
Manzoor Ahmad Sofi - https://orcid.org/0009-0007-4236-8996

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