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Original research article

Clinico-biochemical and Hematological Profile of Multiple Myeloma- a Retrospective Study in a Tertiary Care Hospital in Bihar.

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Abstract

Background: Multiple Myeloma (MM) is a hematological malignancy characterized by clonal proliferation of plasma cells, which produce monoclonal immunoglobulins referred to as M-protein. In this study we aim to study the demographic characteristics and evaluate the clinical, biochemical, hematological and radiological profile of MM in a tertiary care centre in Bihar.

Materials and Methods: Newly diagnosed and previously diagnosed but untreated patients of MM coming to Hematology department over a period of two and a half years (June 2019 to Nov 2021) were included in this retrospective observational study. Diagnosis was confirmed by the Revised International Myeloma Working Group diagnostic criteria. The cases were re-evaluated taking into consideration clinical aspects, biochemical findings, radiological results, hematological profile and bone marrow findings.

Results: During this study a total of 64 cases fulfilled the diagnostic criteria. Mean age of the patients was 55.6 years with a male-to-female ratio of 2.8:1. Most common symptom was generalized weakness (87.5%) followed by backache and other bone pains (80%). 92% patients had anaemia. There were 4 (6.3%) cases of plasma cell leukemia. Albumin-to-globulin ratio was reversed in 83% cases. Hypercalcemia was seen in only 17.2% patients and elevated serum creatinine levels in 47% cases. 80% cases had radiologically detectable abnormalities. On immunotyping most common type was IgG. 9.4% cases had plasmablastic morphology on bone marrow examination. Majority of the cases had interstitial pattern of infiltration. As per Durie-Salmon staging system, majority cases were in stage III (66%).

Conclusion: Most of the patients were in sixth decade of life, but cases as young as 19 years was seen. Generalised weakness and bone pain were the most common presenting symptoms. Majority of patients were in higher stages at the time of diagnosis. The diagnosis of MM requires a systematic approach. Bone marrow aspiration combined with bone marrow biopsy

provides necessary information on the level of bone marrow involvement by plasma cells and its morphological characteristics. They should be employed as a routine procedure in all cases.
Keywords: Multiple myeloma, Monoclonal gammopathy, Plasma cell dyscrasia, Bihar, hematological malignancy.

1.Introduction:

Plasma cell dyscrasias (PCD) are a spectrum of disorders characterized by malignant proliferation of monoclonal plasma cells. This may or may not be accompanied by secretion of monoclonal immunoglobulins known as M-protein. The spectrum of PCD includes Monoclonal gammopathy of undetermined significance (MGUS), Multiple Myeloma (MM), Solitary Plasmacytoma of Bone, Extramedullary Plasmacytoma, Waldenstrom's Macroglobulinaemia, Primary Amyloidosis and Heavy chain Disease.[1]

MM is a disease of malignant plasma cells. It accounts for 1% of all malignant disorders and 10–15% of hematological malignancies. Incidence of MM is 1.1 per 100,000 in Asia and 1.0 per 100,000 in India, whereas in the west it is 4.1/100,000. It typically starts as an asymptomatic precursor condition; either MGUS or smouldering MM. Symptoms can be attributed to CRAB features (hyperCalcemia, Renal failure, Anemia, and Bone lesion).[2-4]

Some of the differences in presentation in India compared to the west are; younger age at diagnosis and higher proportion of patients with anemia. Most patients present with bone pains, anemia, and renal failure.[5,6]

The diagnosis of MM involves assessment of clinical burden of disease, hematological and biochemical analysis, radiological assessment of bone lesions, determination of monoclonal immunoglobulins by serum protein electrophoresis and assessment of plasma cells in the bone marrow or extramedullary tissue. [7] Recent developments and technological advances in assessment of disease include magnetic resonance imaging, immunophenotyping and fluorescent in situ hybridization.[8] However, morphological analysis of bone marrow aspirate and trephine biopsy remains the gold standard for quantifying the plasma cells, assessing the degree of differentiation and pattern of infiltration of the malignant cells.[9] Immunohistochemistry aids to assess clonality of plasma cells. Bone marrow histology correlates well with the clinical stage of MM and offers useful prognostic information. Plasma cell morphology in bone marrow aspirate has significant correlation with clinical stage and survival. [10]

2.Materials and Methods:

The present study is a retrospective observational study conducted at a tertiary care centre in Bihar, over a period of two and a half years (June 2019 to November 2021) after Institutional Ethics Committee clearance.

Patients of suspected or diagnosed MM (prior to starting treatment) coming to Hematology Department were included in the study. Unsuspected cases, diagnosed incidentally on bone

marrow examination were also included. Diagnosis was made on the basis of Revised International Myeloma Working Group diagnostic criteria for multiple myeloma.[11]
The relevant history, clinical data, biochemical parameters and radiological findings were obtained from records. The findings of Hematological investigations such as haemoglobin, total and differential cell counts, erythrocyte sedimentation rate, platelet count, peripheral blood smear (PBS) were obtained. Report of Serum protein electrophoresis to detect M-band was recorded. The Bone Marrow Aspirate (BMA) smears (stained with Leishman's stain) were reviewed. Bone marrow plasma cell percentages were calculated from a 500-cell differential count on conventional Leishman-stained bone marrow aspirate smears by complete scan of the entire smears. In bone marrow biopsy (BMB) sections (if done) percentage of cellular marrow occupied by plasma cells was estimated by examining Hematoxylin and eosin sections. Dominant pattern of plasma cell distribution in the bone marrow was studied. Immunohistochemistry sections (CD38, CD138, kappa and lambda) were studied when available. Complete data was compiled and analysed.

3. Results:
A total of 64 cases of MM were diagnosed during the study period. The age of the patients ranged from 19 to 73 years with a mean of 55.6 years. 47 (73.4%) patients were males and 17 (26.6%) were females with a male-to-female ratio of 2.8:1.
56 (87.5%) had generalized weakness and easy fatigability, 51 (80%) patients presented with backache and other bone pains, 26 (41%) had symptoms of spinal cord compression and 11 (17.2%) had fever.

59 (92%) patients had anaemia as per the criteria satisfying myeloma-related tissue or organ impairement[1] (Hb<10g/dl). 42 (66%) patients had severe anemia (Hb<7g/dl). 5 (8%) patients had thrombocytopenia. Majority of the cases had normal total leukocyte count. 4 (6.3%) patients had leukocytosis. 6 (9.4%) patients had leukopenia out of which 3 (4.7%) patients had pancytopenia.

There were 4 (6.3%) cases of plasma cell leukemia. First was a 19 years old female presenting with weakness, second and third cases were in 6th decade of life and presented with intracranial bleed, and fourth case (55years) presented with generalised weakness.

ESR was elevated in 46 (72%) cases. Albumin-to-globulin ratio was reversed in 53 (83%) cases. Hypercalcemia was seen in 11 (17.2%) patients and elevated serum creatinine levels was present in 30 (47%) cases. 51 (80%) cases had radiologically detectable abnormalities; 39 (61%) had lytic lesions, 21 (33%) had pathological fractures and 20 (31%) had osteoporosis. Of lytic lesions, most frequent area was spine in 25 (39%) cases.

Serum protein electrophoresis was available for 55 patients, of which 51 cases revealed positive M-Band. On immunotyping, (available for 34 patients) the most common type was IgG. Bone marrow plasmacytosis was >10% in all cases. In 15 (23.4%) cases bone marrow examination showed ≥60% plasma cells. 6 (9.4%) cases had plasmablastic morphology (≥2% of plasmablasts). Bone marrow biopsy was done in 38 cases. Majority had interstitial pattern of infiltration (28 cases), 3 had nodular pattern of infiltration, whereas 7 had diffuse pattern. 6 cases were scantly cellular on BMA. The BMB of these cases showed fibrosis with presence of >10% plasma cells.

As per Durie-Salmon staging system;[12] 13 (20%) cases were found to be in stage I, 9 (14%) patients were found to be in stage II and 42 (66%) cases were in stage III.

4. Discussion:

Various studies from India have reported the mean age to be younger by a decade than the west. Individual studies even show considerable adolescent and young adult MM in India. In our study the mean age was 55.6 years. Other hospital-based studies have previously reported similar MM onset in Indian patients (median ~55 years). The reported median MM onset age of in Indians is not only earlier than the West but also quite earlier than that in other Asian countries. Epidemiology and outcomes of MM in India are often different from the West due to an earlier age of onset and limited resources.[13-16]

In our study 92% cases had anemia. Anemia reflects the marrow burden of the disease. It may also be secondary to renal failure. In a developing country like India, anemia may be multifactorial in origin. So relevant investigations (iron profile, RBC indices, peripheral blood smear) should be done to assess the etiology of anemia before attributing it solely to MM.[17] Although anemia is not included in the current revised International Staging System staging, it is a crucial prognostic factor, as presence of anemia at diagnosis leads to significantly poorer overall survival in patients with MM. Thrombocytopenia, which may be due to marrow infiltration by myeloma cells, was observed in 8% cases in our study, as in previous studies.

Hypercalcemia, even though an important diagnostic criterion was seen only in 17.2% patients. Fousad et al and Kyle et al. also reported hypercalcemia only in 18.8% and 13% of patients respectively. Low calcium levels might be due to renal impairment or secondary to Vitamin D deficiency. Hospital based studies have reported certain unique features in Indian MM patients, like greater proportion of anemia and skeletal abnormalities, higher serum creatinine and lesser proportion of hypercalcemia. In this study serum creatinine was elevated in 47% cases. The presence of CRAB features has long been suggested as poor prognostic markers, owing to the end-organ involvement and also as they are manifestations of advanced disease. Serum electrophoresis and subsequent immunotyping showed predominant involvement of IgG, as in other studies. [18-20]

Bone marrow examination provides information on the level of bone marrow involvement by plasma cells and its morphological specificities. BMA is essential for appropriate evaluation of plasma cell differentiation. The cytomorphologic features of plasma cells range from mature to atypical to plasmablastic. On the basis of plasma cell morphology in BMA, myelomas can be classified into mature, intermediary, immature and plasmablastic. Plasmablastic MM is a morphological subset of myeloma, in which the BMA shows ≥2% of plasmablasts. Plasmablasts are characterized by fine reticular nuclear chromatin, large nucleus (greater than 10 μm), large nucleolus (greater than 2 μm), no or very little perinuclear hof and cytoplasm less than one half of the nuclear area. The prevalence of plasmablastic morphology in our study was 9.4%. Many of the previous western studies have shown that plasmablastic morphology of plasma cells in BMA strongly correlates with poor survival. Eastern cooperative oncology group have also confirmed that plasmablastic morphology is a powerful and independent adverse prognostic factor for survival in MM patients.[21-23]

It has been seen that there is a huge variability in the plasma cell percentage being reported, between pathologists for the same patient. So, some experts felt that a combination of BMA, BMB and flow cytometry should be used and highest enumeration of plasma cells of all measurements should be considered.[24] BMA is superior to BMB for identification of plasma cell morphology. However, in cases of fibrosis, BMA yields scantly cellular aspirates and these are preferably estimated in BMB. BMB also enables plasma cell infiltrate classification into

interstitial, nodular and diffuse types. The type of infiltration pattern is in proportion to the stage of the disease. The interstitial and nodular patterns are observed when hematopoiesis is still preserved. In contrast, diffuse infiltration of marrow results in suppression of hematopoiesis. Transformation from interstitial or nodular towards diffuse infiltrate is observed as the disease progresses.[25] IHC (CD38, CD138, kappa and lambda) helps to identify plasma cells and assess their clonality on BMB.

5: Conclusion:

The current study catalogues the demographic characteristics of MM in Bihar. In multiple myeloma, a detailed clinical, biochemical, radiological and hematological assessment along with bone marrow examination renders useful diagnostic and prognostic work-up.

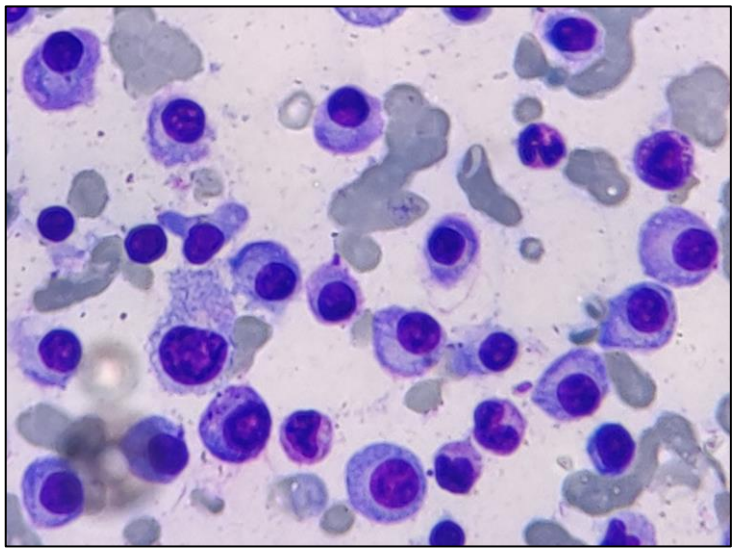

Fig.1: 400x Photomicrograph of bone marrow aspirate showing infiltration by plasma cells (mature and immature forms). Trilineage hematopoiesis is suppressed. Background shows rouleaux formation.

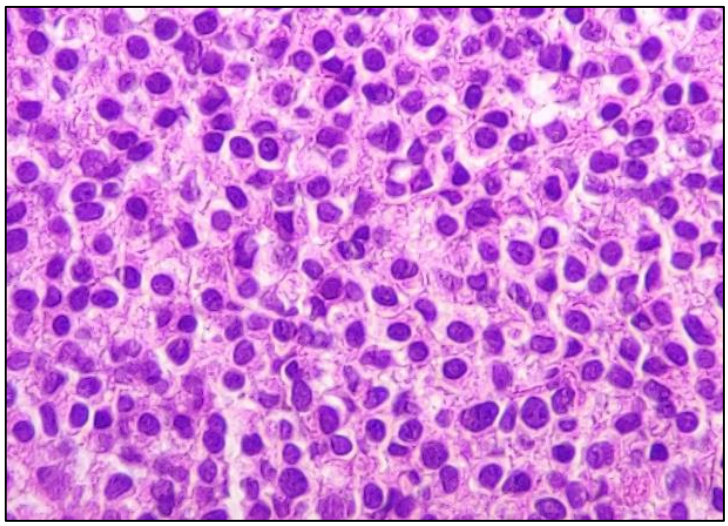

Fig. 2: 100x Photomicrograph of bone marrow biopsy showing interstitial infiltration of plasma cells.

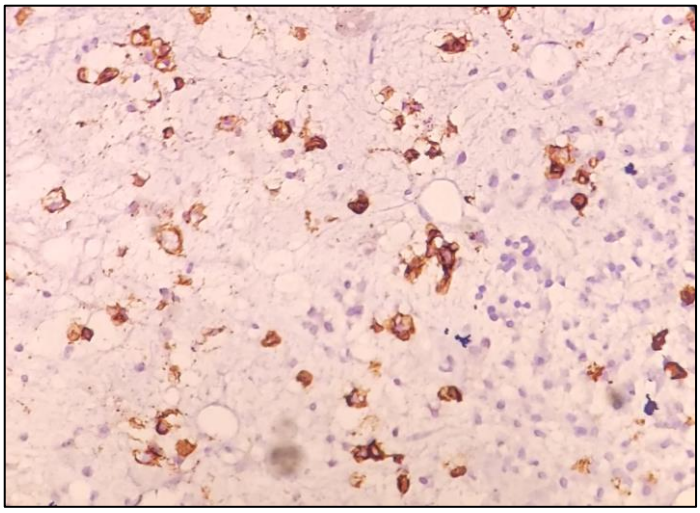

Fig. 3: 100x Photomicrograph showing CD 138 positivity of plasma cells.

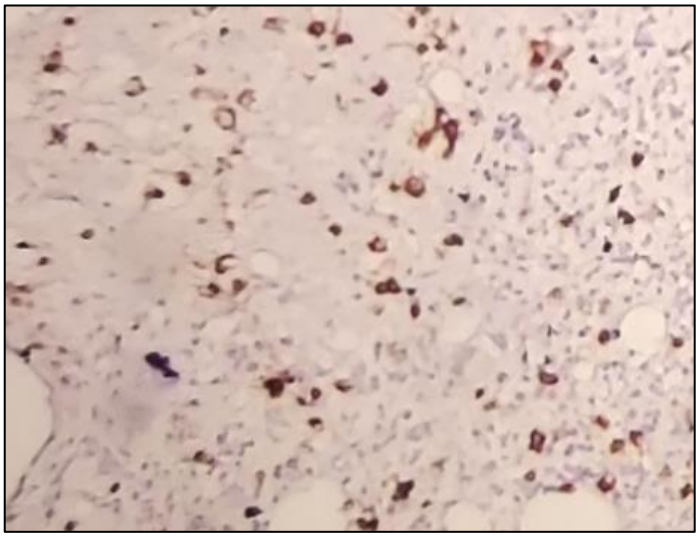

Fig. 4: 100x Photomicrograph showing kappa positivity of plasma cells.

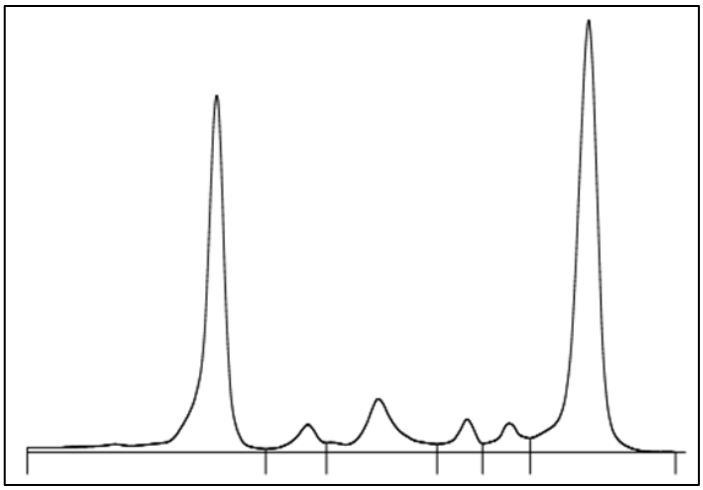

Fig. 5: Serum protein electrophoresis showing M-band in gamma region.

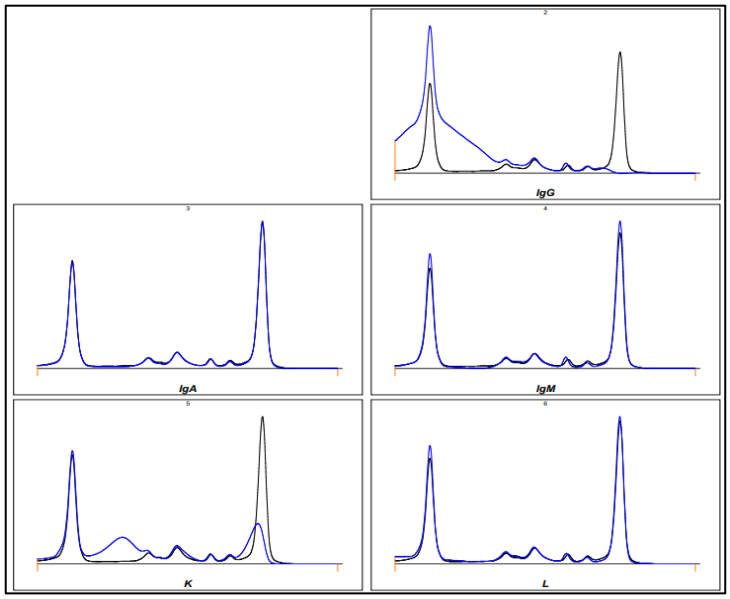

Fig. 6: Immunotyping showing subtraction in IgG and kappa regions.

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