

Decoding the Marrow: Histological Predictors of Advanced Disease in Multiple Myeloma

Sharanjit Singh¹, Sumeena Bajaj¹, Deepti Mutreja², Chinmay Pendharkar¹

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ABSTRACT

Background: Multiple myeloma (MM) is a plasma cell neoplasm (PCN) that is biologically heterogeneous and clinically variable. In addition to cytogenetic and molecular diagnostic tools that are becoming more common in modern risk stratification models, detailed assessment of BM histomorphology remains very accessible, rapid, affordable, and is a valuable tool, especially in a resource-limited setting. Additional studies of prognostic value of marrow cellularity, hematopoietic suppression, cytological differentiation, patterns of infiltration and marrow fibrosis are needed.

Objective: To examine the correlation between the bone marrow histomorphological parameters and clinical disease stages in multiple myeloma patients.

Materials and Methods: This clinicopathological descriptive cross-sectional study was conducted with 103 consecutive newly diagnosed MM patients in an 18-month period in a tertiary care centre in Western India. Marrow aspiration smears and core biopsy specimens were evaluated in a systematic manner with regard to the number of cells, preservation of haematopoiesis, plasma cell differentiation, plasma cell burden, architecture of infiltration and presence of reticulin fibrosis. The staging of each case was done through clinical staging according to the Durie-Salmon staging system.

Results: Among the 103 patients, 48 (46.6%) had stage I, 23 (22.3%) had stage II, and 32 (31.1%) had stage III disease. Adverse histomorphological features were significantly related to the advanced clinical stage. Most patients with hypercellular marrow (90.6%) had stage III disease as compared to those with lower stages ($p = 0.0322$). 75.0% of stage III cases showed suppressed normal trilineage hematopoiesis, while only 12.5% of stage I cases showed suppressed normal trilineage hematopoiesis ($p < 0.00001$). Plasma cell load $> 50\%$ was a significantly strong correlation with advanced disease (62.5% for patients with stage III, 16.7% for stage I, $p = 0.00147$). In general, high grade marrow fibrosis was found most frequently in stage III disease (63.6% of the patients with marrow fibrosis; $p = 0.0177$). The morphology of poorly differentiated cells (plasmablastic) was found only in the cases from stage III.

Conclusions: Profound hematopoietic suppression, high plasma cell burden ($< 50\%$), plasmablastic differentiation and high-grade reticulin fibrosis were strong correlated with advanced clinical stage of MM. Their routine morphological parameters are important baseline prognosticators that can be reported standardised, particularly in the absence of advanced molecular testing.

KEYWORDS: Multiple Myeloma, Bone Marrow Biopsy, Histomorphology, Plasma Cell Infiltration, Bone Marrow Fibrosis.

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Introduction

MM is a hematological malignancy that originates with a transformation of a B-cell into cancerous plasma cells which multiply in the bone marrow cavity without restraint.¹ Normally, plasma cells produce a variety of antibodies to combat infections, but in myeloma clonal expansion of malignant plasma cells drives the hypersecretion of uniform monoclonal immunoglobulins into systemic circulation.² As these malignant cells build-up, they progressively interfere with normal physiology and lead to end organ damage.³ Furthermore, patients have multiple clinical symptoms of active disease including hypercalcemia from bone breakdown, renal impairment due to the deposition of toxin-producing light chains in the renal tubules, a severe anemia from inhibition of normal blood-forming elements, and osteolytic bone lesions that make the bones fragile and prone to fracture.¹⁻³

Affiliation ?

Corresponding Author: Sharanjit Singh

Email: singhsharanjit01@gmail.com

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Although substantial progress has been made in unraveling the molecular pathogenesis of myeloma in recent years, the disease retains remarkable biological and clinical heterogeneity, with patients having varying rates of disease growth, responsiveness to therapy and survival times.⁴ New and updated consensus schemes have introduced

disease serum markers and cytogenetic abnormalities to help predict clinical outcomes in a modern risk-stratified model (International Staging System, ISS; 4, 5). The latter is problematic because the specialized lab instrumentation, costly reagents and technical skills necessary to provide comprehensive cytogenetic and molecular profiling is not always available in under-resourced and developing healthcare environments.⁵ Therefore, conventional microscopic analysis of the bone marrow has been an essential and quick, cost-effective and reliable means of evaluating the burden of disease.⁶

A blood test to determine the total plasma cell percentage,^{6,7} is of little clinical significance compared with a routine bone marrow examination. Aspirate smears are used to obtain cytological information rapidly; however, a trephine core biopsy preserves the cellular architecture and the cellular microenvironment, which provides a good indication of tumour burden and biology.^{7, 8} Several important histomorphological parameters, which can be systematically analyzed under the microscope are evaluated by the pathologist: the level of general cellularity of the marrow cavity, the extent of suppression of the three normal cell lines (erythroid, myeloid, and megakaryocytic), the maturity and cytological differentiation of the plasma cells, the architectural pattern of marrow replacement (interstitial, nodular, or diffuse sheet-like), and the extent and severity of reticulin fiber fibrosis of the marrow stroma.⁶⁻⁸

Several adverse histological features, such as poorly differentiated plasmablastic morphology, diffuse architectural effacement and high-grade reticulin fibrosis, have been shown to be associated with advanced clinical stage and poor clinical outcome, and these parameters are all closely correlated with each other.^{9, 10} The plasmablastic transformation, with visible prominent central nucleoli and high nuclear-to-cytoplasmic ratio is directly correlated with high cell proliferation and genomic instability.¹⁰ Likewise, the development of extensive stromal fibrosis represents progressive microenvironmental changes that may help maintain the existence of tumor cells and result in difficult normalization of the hematopoietic system after treatment, as well as to resistance to treatment.^{9,10} These well-established relationships are, however, not fully explored in Indian patient groups using clinicopathological studies over the whole range of these histomorphological parameters.^{9,10}

Thus the purpose of the present study was to investigate the association between the detailed bone marrow histomorphological alterations and the clinical stage of the disease in newly diagnosed MM patients.

MATERIALS AND METHODS

Study Design and Setting: We conducted descriptive cross sectional clinicopathological study in the Department of

Pathology and Hematology of Western India tertiary care teaching hospital. This study lasted for 18 months.

Study Population: We included in our analysis 103 consecutive patients with a newly diagnosed MM who visited our center during this period.

Inclusion Criteria: MM diagnosed within the last year and having standard clinical work-up, bone marrow morphology and immunophenotypic findings.

Exclusion Criteria:

- People who were already receiving chemotherapy, targeted medications or radiation treatment before marrow sampling.
- Patients referred for whom the direct bone marrow aspirate slides and/or core biopsy blocks are not available for review.

Bone Marrow Evaluation Protocol For all subjects, Marrow aspiration slides prepared with Leishman staining and trephine biopsy tissue sections stained with H&E and Gordon-Sweets silver method for reticulin fiber visualization underwent structured pathological review.

We studied six main microscopic characteristics:

1. Marrow cellularity determined in relation to the patient's age and is either normocellular or hypercellular.
2. Normal Hematopoiesis: Normal blood-forming lines (erythroid, myeloid and megakaryocytic cells) were assessed and determined to be preserved (normal) or suppressed if there was a significant crowding out of the native cells by the tumor cells.
3. Plasma Cell Differentiation: Using the German myeloma task force system, cell maturity was divided into three grades:
 - Well differentiated (plasmacytic): Mature appearance, deep basophilia in the cytoplasm and eccentric/clock-face chromatin.
 - Intermediate differentiation: cells with moderate nuclear changes, somewhat less condensed chromatin and with occasional small nucleoli.
 - Poorly differentiated (plasmablastic): Immature cells with high nuclear to cytoplasmic ratio, loose chromatin, prominent central nucleoli and cell-to-cell variation.
4. **Plasma Cell Burden:** The percent of the intertrabecular marrow space occupied by plasma cells was categorized into $\leq 50\%$ and $> 50\%$ of the marrow.
5. **Pattern of Infiltration:** core biopsies into 4 distribution

styles:

- Interstitial: Loosely clustered myeloma cells in the interstitial space between the normal fat cells and the normal haematopoietic cells.
- Multiple: Numerous rounded plasma cell collections.

Mixed: Nodular clumps with an interspersed spreading pattern.

- Diffuse: Sheets of malignant cells that fully infiltrate the marrow structure.

6. Marrow Fibrosis: The European Consensus system was used to score, whether the silver stained sections contained reticulin fibers and these were classified as either 0, 1 or 2:

- Low grade fibrosis: Grade 0 = normal (fine linear fibers) and Grade 1 = loose fiber intersections.
- High grade fibrosis: Grade 2 = dense and/or diffuse network of reticulin fibres and Grade 3 – dense meshwork with thick coarse collagenous bundles.

Clinical Staging: Each patient was classified as having stage I, II or III disease using the Durie-Salmon system, based on baseline haematocrit, calcium and monoclonal protein concentrations, and on the severity of the skeletal bone lesions seen on imaging tests.

Statistical Analysis: Statistical associations between distinct histomorphological variables and clinical disease stages were evaluated using the Pearson Chi-square test, setting the threshold for statistical significance at a *p*-value below 0.05.

RESULTS

Baseline Clinical Staging

A total of 103 patients were analyzed:

- Stage I: 48 patients (46.6%)
- Stage II: 23 patients (22.3%)
- Stage III: 32 patients (31.1%)

Bone Marrow Cellularity and Clinical Stage

Hypercellularity was identified in 84 cases. Stage III disease demonstrated the highest frequency of hypercellular marrow (29/32, 90.6%) compared with stages I and II ($p=0.0322$).

Hematopoietic Suppression

Suppression of normal marrow elements showed a strong association with disease severity. It was observed in:

Stage I: 6/48 cases (12.5%)

- Stage II: 13/23 cases (56.5%)
- Stage III: 24/32 cases (75%)

This association was highly significant ($p<0.00001$).

Plasma Cell Differentiation

All poorly differentiated/plasmablastic plasma cell forms were observed exclusively in stage III disease, indicating an association between cellular immaturity and advanced disease.

Plasma Cell Burden

High plasma cell infiltration (>50%) was noted in:

- Stage I: 8 cases
- Stage II: 9 cases
- Stage III: 20 cases

Among stage III patients, 62.5% demonstrated >50% marrow infiltration compared with 16.7% of stage I patients ($p=0.00147$).

Pattern of Marrow Infiltration

Interstitial infiltration was the predominant pattern overall. However, mixed and diffuse infiltration patterns were observed mainly among advanced-stage diseases, suggesting greater marrow replacement and aggressive disease biology.

Marrow Fibrosis

High-grade fibrosis was detected in 11 patients:

- Stage I: 1 patient
- Stage II: 3 patients
- Stage III: 7 patients

Approximately, 63.6% of patients with high-grade fibrosis belonged to stage III disease ($p=0.0177$).

Table 1: Correlation of Bone marrow Histomorphological features with clinical stage.

Parameter	Stage I	Stage II	Stage III	<i>p</i> -value
Hypercellularity	34	21	29	0.0322
Suppressed hematopoiesis	6	13	24	<0.00001
Plasma cells >50%	8	9	20	0.00147
High-grade fibrosis	1	3	7	0.0177
Poorly differentiated plasma cells	0	0	13	Significant trend

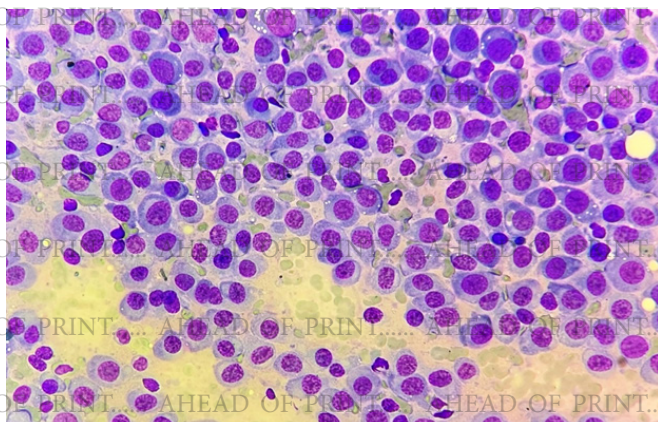


Figure 1: Bone marrow aspirate showing sheets of plasma cells with few atypical forms (leishman stain 100x).

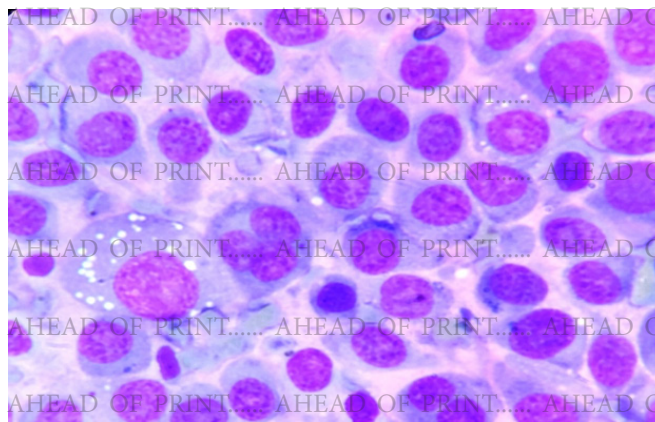


Figure 2: Bone marrow aspirate showing binucleate and trinucleate plasma cells (leishman stain 400x).

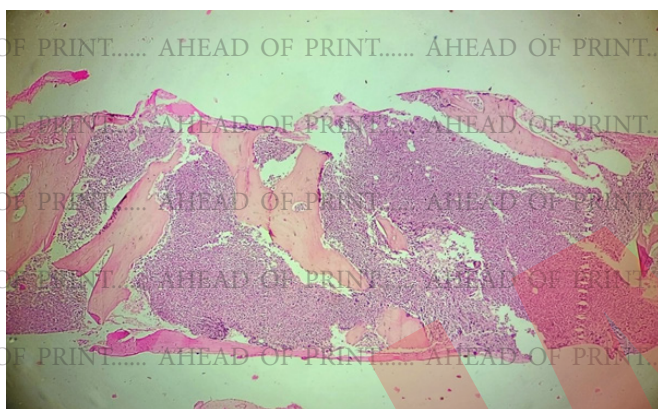


Figure 3: Bone marrow biopsy showing interstitial infiltration of plasma cells (h & e stain 40x).

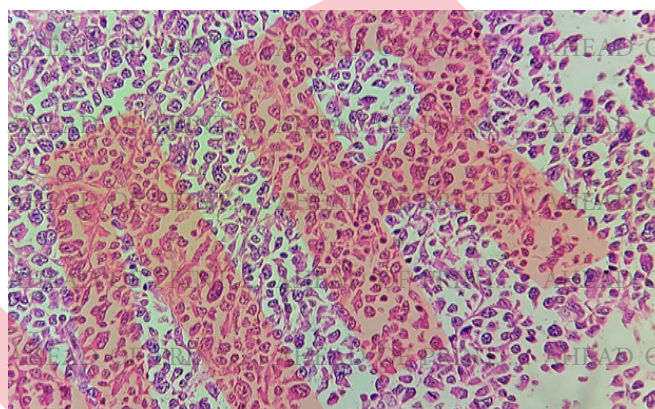


Figure 4: Bone marrow biopsy showing well differentiated myeloma with interstitial infiltration of plasma cells (h&e stain 400x).

DISCUSSION

The results of this study showed that a comprehensive, multiparametric analysis of the histomorphological features of bone marrow can provide clinically significant prognostic information that is more than simply the plasma cell percentage. The advantages of bone marrow aspirate smears are the rapid availability of cytological diagnosis, but trephine core biopsies retain the architectural association of not only neoplastic plasma cells but also of marrow microenvironment. In the newly diagnosed cohort, hypercellular marrow spaces, marked suppression of endogenous haematopoiesis, marked tumour bulk (>50%) and poor differentiation of the cytomorphology and high-grade reticulum fibrosis was the signature of advanced clinical disease (Durie-Salmon III criteria). As plasmablastic morphology was closely linked with advanced clinical stage, it points to the biological aggressiveness of the immature plasma cells (11-13, 19, 20). The poorly differentiated forms exhibit high N:C ratio, fine dispersed chromatin, prominent nucleoli and rapid mitotic activity, indicative of rapid proliferation, loss of terminal differentiation and underlying genomic instability (11-13). Because

plasmablastic features were only found in Stage III cases, routine cytological grading may be used as an immediate morphological surrogate for high-risk tumor biology. Likewise, the diffuse growth pattern and extensive marrow infiltration (>50%) closely reflect the physical displacement and the destruction of the normal niche microenvironment. The significant differences in the degree of trilineage hematopoietic suppression observed between the clinical stages is explained by the structural replacement. Analyzing the stromal fibrosis in addition to the crowding effect, it was evident that the stromal fibrosis was present in high-grade stages at higher frequencies (63.6% of fibrotic cases in Stage III) and it is a strong sign of microenvironmental reactive remodeling in the tumor, the presence of which is evident from the association of fibrotic and non-fibrotic cases in the studied cohorts.^{21, 22} Excessive reticulin fiber deposition caused by the action of malignant plasma cells on the surrounding stromal fibroblasts and its release of the pro-fibrotic cytokines. This highly cellular stromal meshwork can cause a loss of residual blood cell production also provide a sanctuary for the sibs of plasma cells which in turn results in poor therapeutic delivery and resistance.^{22, 23} Modern prediction risk stratification models are largely

based on FISH panels and next-generation sequencing technologies but these are more costly, technically complex and not widely available beyond peripheral hospital centers (PHCs) and in LMICs (14, 15, 21, 24). Under such conditions of limited resources, the light microscopic analysis of bone marrow aspirate and/or core biopsy is a relatively quick, inexpensive, and highly reproducible diagnostic option.^{24,25}

This gap of diagnosis can be bridged by using a standardized reporting format that systematically records marrow cellularity, hematopoietic suppression, differentiation of marrow cells, patterns of marrow infiltration, and reticulin fibrosis, which will assist clinicians in early risk stratification, both at diagnosis and follow-up.^{22,25} The major advantage of our study is simultaneous evaluation of multiple histopathological markers in a well-defined group of 103 consecutive treatment naive patients referred to a tertiary care teaching center (16-18). However, some restrictions need to be recognised. First, it was a single-center, cross-sectional, observational study with no long-term patient follow-up, so it was not possible to directly perform survival analysis for progression-free survival (PFS) and overall survival (OS). Second, routine cytogenetic and molecular risk stratification were not done simultaneously and so there was no direct statistical correlation between the specific adverse genetic abnormality and the individual histological feature. Further prospective studies with standardized histomorphology and molecular testing in multi-center prospective studies will further elucidate the best way to integrate these easily available morphological markers with molecular risk factors.

CONCLUSION

Histomorphologic analysis of bone marrow is a very useful clinical and prognostic tool in newly diagnosed multiple myeloma. The correlated adverse histological markers – all of them marked hematopoietic suppression, high plasma cell burden over 50%, poorly differentiated plasmablastic morphology, diffuse infiltration and high grade reticulin fibrosis – have high correlations with advanced Durie-Salmon clinical stage. The consistent reporting of these parameters will enable access to a practical and cheap tool for risk stratification, especially in the clinical environment where there is a lack of advanced molecular testing.

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Orcid ID:Sharanjit Singh - <https://orcid.org/0000-0001-8149-6797>Sumeena Bajaj - <https://orcid.org/0000-0002-9719-2489>Deepti Mutreja - <https://orcid.org/0000-0001-6274-4863>Chinmay Pendharkar - <https://orcid.org/0000-0003-1869>