

Correlation between Bone Marrow Plasma Cell Morphology and Cytogenetic Abnormalities in Multiple Myeloma Patients

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Abstract

Background: Multiple Myeloma (MM) is a plasma cell malignancy characterized by clonal proliferation in the bone marrow, leading to anemia, bone lesions, hypercalcemia, renal dysfunction, and monoclonal protein production. Recent advances highlight the importance of cytogenetic abnormalities as key prognostic indicators. **Aim:** This study was undertaken to evaluate the relationship between bone marrow plasma cell morphology and cytogenetic abnormalities in MM patients.

Materials and Methods: This hospital-based cross-sectional observational study included 100 diagnosed cases of multiple myeloma with available cytogenetic data. Bone marrow aspiration and biopsy samples were analyzed for plasma cell percentage, morphological subtype (plasmacytic, plasmablastic, mixed), and infiltration pattern (nodular, interstitial, diffuse). Cytogenetic evaluation was performed using Fluorescence In Situ Hybridization (FISH) and GTG banding. Statistical analysis was conducted using SPSS, and a p-value < 0.05 was considered significant.

Results: A statistically significant association was observed between cytogenetic abnormalities and plasma cell characteristics ($p < 0.05$). The majority of cases demonstrated a high plasma cell burden (>50%), particularly in those with del(13q14.3) and complex karyotype. Plasmacytic morphology predominated in cases with normal cytogenetics and t(11;14), whereas plasmablastic morphology was more commonly associated with cytogenetic abnormalities, especially complex karyotypes. Diffuse bone marrow infiltration was the most common pattern (52%) and was predominantly associated with high-risk abnormalities such as del(17p13), t(4;14), and t(14;16). In contrast, t(11;14) was associated with nodular and interstitial patterns.

Conclusion: Plasma cell morphology, marrow infiltration pattern, and cytogenetic abnormalities show a significant correlation in multiple myeloma. Their combined evaluation enhances understanding of disease biology and may improve prognostic stratification and clinical management.

Keywords: Multiple Myeloma; Plasma Cells; Cytogenetics; FISH; Bone Marrow Morphology.

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Introduction

Multiple Myeloma (MM) is a type of cancer affecting plasma cells, marked by symptoms such as anemia, the presence of monoclonal protein in serum and/or urine, bone lesions, hypercalcemia, and kidney insufficiency. It constitutes 1% of all malignancy types and 10-15% of all hematological malignancies [1]. It occurs more frequently in men than in women (1.4:1).

The clinical manifestations arise from the infiltration of plasma cells into the tissue, monoclonal protein secretion, and immune system

impairment. As a result of renal damage and the substitution of bone marrow with plasma cells, anaemia develops. Its manifestations include fatigue and pallor, among others. In 80% of cases, the presenting manifestation is bone pain. Osteoclastic bone resorption is on the rise, resulting in a significant disruption of bone formation [2]. A diagnosis and patient stratification into good, intermediate, and poor prognosis groups necessitate multiple investigations [3].

Traditionally employed investigations encompass

peripheral blood smear, erythrocyte sedimentation rate, serum calcium and creatinine levels, serum albumin levels, and bone marrow aspirate analysis (where myeloma cells of varying maturity—ranging from mature to immature, pleomorphic, and plasmablastic forms—are observed). In addition, a bone marrow biopsy is performed, revealing plasma cells in focal nodules, interstitial clusters, and diffuse sheets. M-component on Serum Protein Electrophoresis and immunofixation electrophoresis are performed to differentiate immunoglobulin classes, while skeletal survey for bone destruction, β 2M levels [4].

However, in recent times, cytogenetic abnormalities have come to be seen as strong prognostic factors in myeloma [5]. Currently, tumours are stratified into high, intermediate, and standard risk disease using a combination of conventional cytogenetics and interphase Fluorescence In-Situ Hybridisation (FISH). Such classification can assist in directing therapy. FISH is utilized for the identification of t(11;14), t(6;14), t(4;14), t(14;16), t(14;20), del17p13, del13, 1q+, and trisomies involving odd-numbered chromosomes.⁶The present study was conducted to compare the morphological details of plasma cells with cytogenetic abnormalities.

Aim & Objectives

Aim: To evaluate the relationship between bone marrow plasma cell morphology, plasma cell percentage, and cytogenetic abnormalities in patients with Multiple Myeloma.

Objectives

Primary Objective: To assess the association between cytogenetic abnormalities and plasma cell morphology in bone marrow.

Secondary Objectives

- To correlate plasma cell percentage on bone marrow aspiration with cytogenetic findings.
- To evaluate the relationship between cytogenetic abnormalities and morphological subtype (plasmacytic, plasmablastic, mixed).
- To study the association between cytogenetic abnormalities and bone marrow infiltration pattern (nodular, interstitial, diffuse).
- To identify patterns suggestive of disease aggressiveness based on combined morphological and cytogenetic parameters.

Materials & Methods

Study Design: This was a hospital-based cross-sectional observational study conducted to evaluate the relationship between bone marrow plasma cell morphology and cytogenetic abnormalities in patients with Multiple Myeloma.

Study Population: The study included 100 patients diagnosed with multiple myeloma of both genders. All patients underwent detailed clinical, hematological, morphological, and cytogenetic evaluation.

Study Setting: The study was conducted in the Department of Pathology, Anugrah Narayan Magadh Medical College & Hospital, Gaya Ji, Bihar, India with cytogenetic analyses outsourced to accredited external laboratories.

Study Period: The study was carried out over a period of one year and six months, from July 2024 to December 2025.

Ethical Considerations

- The study was conducted after obtaining approval from the Institutional Ethics Committee (IEC) of Nalanda Medical College, Patna.
- Written informed consent was obtained from all participants prior to inclusion in the study.
- Confidentiality of patient data was strictly maintained throughout the study.
- The study adhered to the ethical principles outlined in the Declaration of Helsinki.

Inclusion Criteria

- All newly diagnosed and previously diagnosed cases of multiple myeloma.
- Patients of both genders and all age groups.
- Availability of complete clinical, hematological, morphological, and cytogenetic data.

Exclusion Criteria

- Diagnosed cases of multiple myeloma in which cytogenetic data was not available.
- Inadequate or poorly preserved bone marrow or peripheral smear samples.

Methodology

Clinical Evaluation: A detailed clinical history was obtained for each patient, including presenting symptoms, duration of illness, and relevant past medical history. Thorough physical examination findings were recorded.

Sample Collection

- Peripheral blood samples and bone marrow aspirates were collected under aseptic precautions.
- Bone marrow biopsy specimens were also obtained where indicated.

Morphological Analysis

- Peripheral blood smears and bone marrow aspirate smears were stained using Giemsa stain.

- Smears were examined under light microscopy and plasma cells were categorized into:
1. **Mature Plasma Cells**
 - Round to oval eccentric nucleus
 - “Spoke-wheel” chromatin pattern
 - Abundant basophilic cytoplasm with a prominent perinuclear hof.
 2. **Immature Plasma Cells**
 - Dispersed nuclear chromatin
 - Increased nuclear-to-cytoplasmic ratio
 - Prominent nucleoli
 3. **Plasmablasts**
 - Diffuse chromatin pattern
 - Nuclear diameter >10 µm or nucleolus >2 µm
 - Centrally placed nucleus
 - Scant cytoplasm with minimal or absent perinuclear hof

Classification of Myeloma

Based on the proportion of plasmablasts:

- **Plasmacytic type:** Plasmablasts <15%
- **Plasmablastic type:** Plasmablasts >50%
- **Mixed type:** Plasmablasts 15–50%

Histopathological Examination

- Bone marrow biopsy sections were stained with Haematoxylin and Eosin (H&E).
- The pattern of plasma cell infiltration was categorized as:
 1. Nodular
 2. Interstitial
 3. Diffuse

Bone marrow aspiration and biopsy

- Bone marrow aspiration and biopsy were performed under local anesthesia, typically from the posterior superior iliac spine using standard sterile techniques.
- Aspirated material was immediately smeared on glass slides and processed for staining.
- Biopsy specimens were fixed in formalin and processed for histopathological examination.

Investigations

Cytogenetic Analysis

- Cytogenetic studies were performed using:
 1. Fluorescence In Situ Hybridization (FISH)

2. GTG (Giemsa Trypsin G-banding) karyotyping

FISH Panel Included

- del(17p13)
- del(13q14.3)
- t(4;14)
- t(11;14)
- t(14;16)

Reports obtained from external laboratories were systematically recorded and correlated with morphological findings.

Outcome Measures

Primary Outcome: Correlation between plasma cell morphology and cytogenetic abnormalities.

Secondary Outcomes

- Association between plasmablastic morphology and high-risk cytogenetic markers.
- Correlation between bone marrow infiltration pattern and cytogenetic profile.
- Distribution of morphological subtypes among study participants.

Statistical Analysis: Data were entered into Microsoft Excel and analyzed using SPSS (IBM Corp., Chicago, IL, USA).

Descriptive Statistics

- Continuous variables were expressed as mean ± standard deviation (SD).
- Categorical variables were expressed as frequency and percentage (%).

Inferential Statistics

- Chi-square (χ^2) test was used to assess associations between categorical variables (e.g., morphology vs cytogenetic abnormalities).
- Analysis of Variance (ANOVA) was applied to compare means among multiple groups where applicable.
- Fisher’s exact test was used when expected cell counts were small.

Level of Significance: A p-value < 0.05 was considered statistically significant.

Results

Table 1: Comparison of cytogenetics with plasma cells on bone marrow aspiration

Cytogenetics		Plasma cells			P value
		<20%	20-50%	>50%	
FISH (65)	Normal genome (50)	4	12	34	0.01
	Positive for del13q14.3 (10)	1	3	6	
	Positive for t (11,14) (5)	0	1	4	
GTG Banding (35)	Normal Karyotype (26)	1	2	23	0.02
	Increase in heterochromatin (7)	0	2	5	
	Complex Karyotype (2)	0	0	2	

Table 1 and figure 1, show that, a statistically significant association was observed between cytogenetic abnormalities and plasma cell percentage ($p < 0.05$). Among cases evaluated by FISH ($n = 65$), the majority of patients with a normal genome (50 cases) demonstrated a high plasma cell burden, with 34 cases showing $>50\%$ plasma cells, 12 cases showing 20–50%, and only 4 cases showing $<20\%$ plasma cells. This indicates that even in cytogenetically normal cases, a substantial proportion of patients had significant marrow infiltration.

Among cases positive for del(13q14.3) (10 cases), a similar trend was observed, with the majority (6 cases) showing $>50\%$ plasma cells, followed by 3 cases with 20–50% and 1 case with $<20\%$ plasma cells. This suggests an association between this abnormality and increased tumor burden. In cases with t(11;14) (5 cases), most patients (4 cases) had $>50\%$ plasma cells, while 1 case had 20–50% plasma cells and none had $<20\%$, indicating a

predominance of higher marrow infiltration even in this cytogenetic subtype.

In the GTG banding group ($n = 35$), among 26 cases with a normal karyotype, the majority (23 cases) showed $>50\%$ plasma cells, while only 2 cases had 20–50% and 1 case had $<20\%$ plasma cells. All 7 cases with increased heterochromatin showed moderate to high plasma cell percentages, with 5 cases having $>50\%$ and 2 cases having 20–50%, and none having $<20\%$.

Notably, both cases with complex karyotype demonstrated $>50\%$ plasma cells, indicating a strong association between complex cytogenetic abnormalities and high tumor burden.

Overall, the findings suggest that higher plasma cell percentages ($>50\%$) are predominantly associated with both normal and abnormal cytogenetic profiles, but are especially prominent in cases with cytogenetic abnormalities such as del(13q14.3) and complex karyotype.

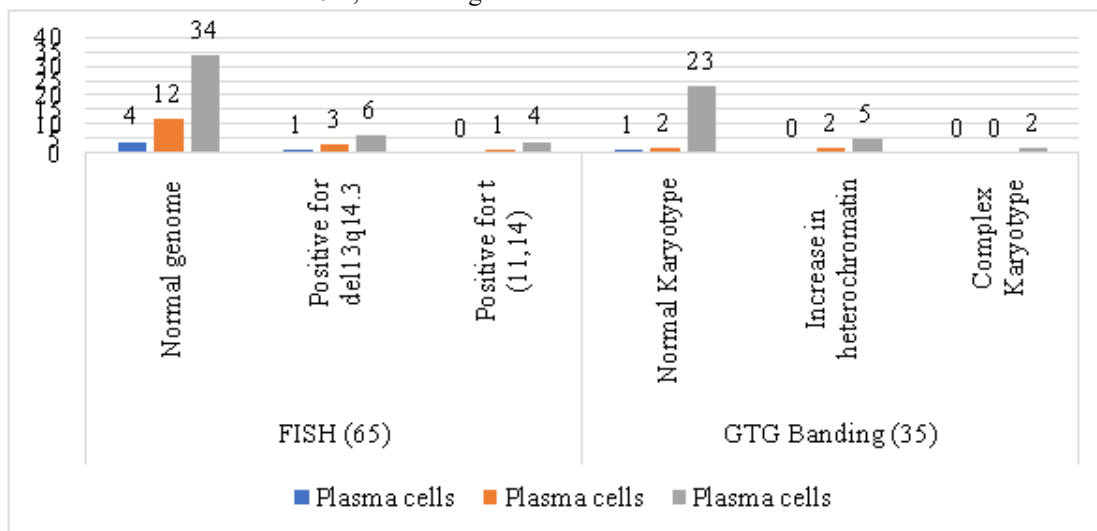


Figure 1: Comparison of cytogenetics with plasma cells on bone marrow aspiration

Table 2: Comparison of cytogenetics with morphological type of myeloma

Cytogenetics	Plasma cells			P value	
	Plasmacytic	Plasma-blastic	Mixed		
FISH (65)	Normal genome (50)	42	0	8	0.03
	Positive for del13q14.3 (10)	5	2	3	
	Positive for t(11,14) (5)	5	0	0	
GTG Banding (35)	Normal Karyotype (26)	20	0	6	0.01
	Increase in heterochromatin (7)	7	0	0	
	Complex Karyotype (2)	1	1	0	

Table 2 shows that, a statistically significant relationship was observed between cytogenetic findings and morphological subtype of plasma cells ($p < 0.05$). Among the cases analyzed by FISH ($n = 65$), the majority of patients with a normal genome (50 cases) exhibited plasmacytic morphology, seen in 42 cases, while none showed plasmablastic

morphology and 8 cases demonstrated a mixed pattern. This indicates that normal cytogenetic profiles are predominantly associated with more differentiated, less aggressive plasma cell morphology. In cases positive for del(13q14.3) (10 cases), a more varied distribution was observed, with 5 cases showing plasmacytic morphology, 2

cases showing plasmablastic morphology, and 3 cases demonstrating a mixed pattern. This suggests that del(13q14.3) may be associated with intermediate morphological behavior, reflecting a spectrum of disease activity. All 5 cases positive for t(11;14) demonstrated exclusively plasmacytic morphology, with no cases showing plasmablastic or mixed types. This finding supports the association of t(11;14) with a more mature plasma cell phenotype and relatively favorable disease biology. In the GTG banding group (n = 35), similar trends were observed. Among 26 cases with

a normal karyotype, 20 cases showed plasmacytic morphology and 6 showed a mixed pattern, with no plasmablastic cases identified. All 7 cases with increased heterochromatin demonstrated plasmacytic morphology, further reinforcing the predominance of mature plasma cells in less complex cytogenetic profiles. In contrast, among the 2 cases with complex karyotype, one case showed plasmacytic morphology while the other demonstrated plasmablastic morphology, indicating a shift toward a more aggressive cellular phenotype in the presence of complex genetic abnormalities.

Table 3: Association between Cytogenetic Abnormalities and Bone Marrow Infiltration Pattern in Patients with Multiple Myeloma (n = 100)

Cytogenetic Abnormality	Nodular (n, %)	Interstitial (n, %)	Diffuse (n, %)	Total (n, %)	χ^2 value	p-value
del(17p13)	2 (10.0%)	4 (20.0%)	14 (70.0%)	20 (100%)	18.42	0.001*
del(13q14.3)	5 (16.7%)	10 (33.3%)	15 (50.0%)	30 (100%)	9.36	0.009*
t(4;14)	1 (6.7%)	3 (20.0%)	11 (73.3%)	15 (100%)	14.11	0.002*
t(11;14)	10 (40.0%)	10 (40.0%)	5 (20.0%)	25 (100%)	11.27	0.004*
t(14;16)	1 (10.0%)	2 (20.0%)	7 (70.0%)	10 (100%)	10.05	0.006*
Total	19 (19.0%)	29 (29.0%)	52 (52.0%)	100 (100%)		

Table 3 demonstrates the diffuse pattern of infiltration was the most common overall, observed in 52% of cases, followed by interstitial (29%) and nodular patterns (19%). A clear variation in infiltration pattern was noted across different cytogenetic abnormalities, and this association was found to be statistically significant ($p < 0.05$).

Among high-risk cytogenetic abnormalities, del(17p13) showed a marked predominance of diffuse infiltration, seen in 70% of cases, with only 20% and 10% showing interstitial and nodular patterns respectively ($\chi^2 = 18.42$, $p = 0.001$). Similarly, t(4;14) demonstrated diffuse infiltration in 73.3% of cases, with minimal nodular involvement (6.7%), indicating its strong association with aggressive marrow involvement ($\chi^2 = 14.11$, $p = 0.002$). t(14;16) also followed a comparable trend, with 70% of cases showing diffuse infiltration ($\chi^2 = 10.05$, $p = 0.006$).

In contrast, t(11;14) exhibited a different pattern, with nodular and interstitial infiltration each accounting for 40% of cases, and only 20% showing diffuse involvement ($\chi^2 = 11.27$, $p = 0.004$). This suggests a relatively less aggressive pattern of marrow infiltration associated with this cytogenetic subtype. The abnormality del(13q14.3) showed a more heterogeneous distribution, with 50% of cases demonstrating diffuse infiltration, 33.3% interstitial, and 16.7% nodular pattern ($\chi^2 = 9.36$, $p = 0.009$), indicating an intermediate behavior.

Discussion

In the present study, a statistically significant association was observed between cytogenetic abnormalities and plasma cell percentage on bone marrow aspiration ($p < 0.05$). Among patients evaluated by FISH, the majority of cases with a normal genome showed >50% plasma cells (68%), while cases positive for del(13q14.3) and t(11;14) also demonstrated a predominance of higher plasma cell burden. Similarly, in GTG banding, cases with normal karyotype predominantly showed >50% plasma cells (88.5%), while all cases with complex karyotype demonstrated >50% plasma cell infiltration, indicating a strong association with disease burden. These findings are consistent with the study by Kumar et al. (2021), who reported that higher plasma cell percentages (>50%) were significantly associated with cytogenetic abnormalities, particularly complex karyotypes and chromosomal deletions, suggesting increased tumor load and aggressive disease biology [7]. A study by Li et al. (2020) also demonstrated that patients with adverse cytogenetic profiles had significantly higher marrow plasma cell infiltration, supporting the correlation between tumor burden and genetic abnormalities [8].

Furthermore, Mohan et al. (2022) observed that complex karyotypes were almost exclusively associated with high plasma cell percentages (>50%), indicating poor prognosis and advanced disease stage [9].

We found that in Multiple Myeloma, among FISH cases (n = 65), normal genome (n = 50) showed plasmacytic, plasmablastic, and mixed morphology in 42, 0, and 8 cases, respectively. Among cases positive for del(13q14.3) (n = 10), the distribution

was 5, 2, and 3 cases, respectively. All cases with t(11;14) (n = 5) showed plasmacytic morphology.

In GTG banding (n = 35), normal karyotype (n = 26) showed plasmacytic, plasmablastic, and mixed morphology in 20, 0, and 6 cases, respectively. All cases with increased heterochromatin (n = 7) were plasmacytic, while among complex karyotype cases (n = 2), one was plasmacytic and one was plasmablastic. Most cases with normal cytogenetics (FISH and GTG banding) exhibited plasmacytic morphology, whereas plasmablastic morphology was more frequently associated with cytogenetic abnormalities such as del(13q14.3) and complex karyotype. Notably, all cases with increased heterochromatin showed plasmacytic morphology, while complex karyotype showed a mix of plasmacytic and plasmablastic forms, suggesting progression towards aggressive disease.

These findings are supported by Singh et al. (2023), who reported that plasmablastic morphology was significantly associated with cytogenetic abnormalities and adverse prognostic markers, whereas plasmacytic morphology correlated with standard-risk cytogenetics [10].

Similarly, Zhang et al. (2021) demonstrated that plasmablastic variants were associated with higher proliferative indices and cytogenetic abnormalities, including deletions and translocations, indicating aggressive clinical course [11]. A study by Patel et al. (2022) also found that plasmacytic morphology predominated in cases with normal cytogenetics, while plasmablastic morphology was more common in patients with complex cytogenetic abnormalities [12]. In the present study, a statistically significant association was observed between cytogenetic abnormalities and bone marrow infiltration pattern ($p < 0.05$). The diffuse pattern was the most common overall (52%), particularly in high-risk cytogenetic abnormalities such as del(17p13), t(4;14), and t(14;16), where diffuse infiltration was seen in 70–73.3% of cases.

In contrast, t(11;14) was associated with nodular and interstitial patterns (40% each), indicating less aggressive marrow involvement. Del(13q14.3) showed an intermediate pattern distribution.

These findings are in agreement with Sharma et al. (2022), who reported that diffuse marrow infiltration was significantly associated with high-risk cytogenetic abnormalities, including del(17p) and t(4;14), reflecting aggressive disease biology [13].

Similarly, García-Sanz et al. (2021) observed that diffuse infiltration pattern correlated with increased tumor burden and adverse cytogenetics, while nodular patterns were more common in standard-risk disease [14].

A study by Rao et al. (2023) also demonstrated that patients with t(11;14) frequently showed nodular or interstitial infiltration, suggesting a relatively favorable prognosis compared to other cytogenetic abnormalities [15].

Limitations of the Study

- **Sample Size:** The study included a relatively small sample size (n = 100), which may limit generalizability.
- **Single-Centre Study:** Conducted at a single tertiary care center, which may not represent the broader population.
- **Limited Cytogenetic Panel:** Only selected abnormalities (del17p13, del13q14.3, t(4;14), t(11;14), t(14;16)) were studied; other important abnormalities (e.g., 1q gain, trisomies) were not included.
- **Outsourced Cytogenetic Analysis:** Variability in reporting from external laboratories may introduce bias.
- **Cross-Sectional Design:** Lack of follow-up data prevented assessment of survival outcomes and treatment response.
- **Subjective Morphological Assessment:** Morphological classification may have inter-observer variability.

Conclusion

Authors found that the present study demonstrated a statistically significant association ($p < 0.05$) between cytogenetic abnormalities and plasma cell characteristics in Multiple Myeloma. Higher plasma cell percentages (>50%) were predominantly observed across both normal and abnormal cytogenetic groups, with a particularly strong association in cases with del(13q14.3) and complex karyotype, indicating increased tumor burden. Plasmacytic morphology was most commonly associated with normal cytogenetic profiles and t(11;14), suggesting a relatively favorable biological behavior, whereas plasmablastic morphology was more frequently associated with cytogenetic abnormalities, especially complex karyotypes, indicating aggressive disease. A significant correlation was also observed between cytogenetics and bone marrow infiltration pattern, with diffuse infiltration predominating in high-risk abnormalities such as del(17p13), t(4;14), and t(14;16), while nodular and interstitial patterns were more commonly seen in t(11;14). Overall, the findings indicate that plasma cell morphology, marrow infiltration pattern, and cytogenetic abnormalities are closely interrelated, and their combined evaluation provides a more comprehensive understanding of disease behavior and prognosis.

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