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Cytogenetics of Multiple Myeloma

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Abstract

Multiple myeloma is a type of cancer that affects the plasma cells in the bone marrow. In this abstract, we discuss the cytogenetic abnormalities in multiple myeloma patients and their correlation with age and gender. We also describe the techniques used for cytogenetic analysis in the Indian population. Our study included 70 patients with multiple myeloma, and cytogenetic analysis was performed using conventional karyotyping and Fluorescence In-situ Hybridization (FISH) techniques. We observed a higher incidence of cytogenetic abnormalities in patients above 60 years of age, with male predominance. FISH analysis showed a higher detection rate of cytogenetic abnormalities compared to conventional karyotyping. FISH also provided additional information on the extent and complexity of the chromosomal aberrations. It is a cytogenetic technique that uses fluorescently labelled probes to detect genetic abnormalities in the chromosomes of cells obtained from bone marrow. This analysis can provide valuable information about the type and stage of the disease, Translocations t(4;14),t(14;16), t(6;14), and t(14;20) were associated with anaemia, t(4;14) was associated with a higher serum monoclonal protein and plasma cell proliferation. Monosomy 13 is associated with a short survival rate with transition monoclonal gammopathy. In conclusion, our study confirms the age and male predominance in multiple myeloma and highlights the importance of cytogenetic analysis in the diagnosis and prognosis of the disease. By studying the chromosomal abnormalities in MM, we can gain insights into the underlying causes of the disease. In this study, we will discuss the cytogenetics of MM and explore how it can help understand the genetics of cancer. The study highlights the chromosomal abnormalities associated with MM and its implications for diagnosis and prognosis.

Keywords: Fluorescence in situ hybridisation; Chromosomal translocations; Plasma cell.

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INTRODUCTION

Multiple myeloma is a type of cancer that affects plasma cells, a type of white blood cell found in the bone marrow. It is the second most common blood cancer after lymphoma. Multiple myeloma is a malignant neoplasm of plasma cells that accounts for approximately 10% of all hematologic malignancies and is characterized by clonal proliferation of abnormal plasma cells in the bone marrow. (Rajkumar and Kumar, 2016).

The pathogenesis of multiple myeloma involves

complex interactions between the malignant plasma cells and the bone marrow micro environment. (Palumbo and Anderson, 2011).

Chromosome abnormalities are detected in almost all cases of multiple myeloma, with a wide range of frequency and prognostic significance (Mikulasova *et al*., 2021).

Cytogenetic abnormalities are present in approximately 50-60% of patients with MM and have a significant impact on prognosis and treatment outcomes. (Kumar *et al.*, 2021). The most common cyto genetic abnormalities in MM are hyper diploid, t(11;14), t(4;14), and del (17p), which are associated with different clinical features and outcomes. (Chng and Gasparetto, 2020). Hyperdiploidy, defined as a modal chromosome number >46, is present in approximately 50% of patients with MM and is associated with a favourable prognosis. (Avet-Loiseau *et al*., 2021).

t(11;14) is present in approximately 15-20% of patients with MM and is associated with a better response to therapy and longer progression free and overall survival. (Dimopoulos *et al*., 2021). t(4;14) is present in approximately 15% of patients with MM and is associated with a poor prognosis, resistance to treatment, and shorter overall survival. (Kumar *et al*., 2021). del(17p) is present in approximately 10-15% of patients with MM and is associated with a poor prognosis and resistance to treatment. (Chng and Gasparetto, 2020).

Cytogenetic studies have shown that multiple myeloma is a heterogeneous disease with a complex karyotype involving various numerical and structural aberrations. The most common cytogenetic abnormality is hyper diploid, which is present in approximately 50% of cases and is associated with a favourable prognosis." (Avet Loiseau *et al*., 2007). Translocation (11;14)(q13; q32) Is the most frequent cytogenetic abnormality in multiple myeloma and is present in approximately 15-20% of cases.

AIMS & OBJECTIVES

To identify and study the cytogenetic alteration in multiple myeloma patients in the Indian population.

Objectives

1. Highlight the age of occurrence (60 & above).
2. To Correlate Male Predominance with MM.

MATERIAL & METHODS

Source: Subjects were referred for MM from the St. John's Medical College and Hospital Bangalore in patient oncology unit from time period of April 2022 to May 2023. Institutional ethical clearance from Institutional Ethics Committee of St. Johns' Medical College and Informed consent from patients were obtained.

Cytogenetic analysis was carried out using short term bone marrow cultures with RPMI 1640 and incubation at 37°C and 5% CO_2 for all Multiple myeloma cases. Cells were harvested with colchemid and fixed cell suspension was dropped on to slides. Slides were subjected to GTG banding for Karyotyping and FISH analysis using specific FISH probes for MM.

FISH probe panel Included

XLDLEU/LAMP- 13q del
XLTP53/17CEN-P53 del
XLIGHBA-IGH Break a part
MYEON/IGHDF- t(11;14)
FGFR3/IGH-XL t(4;14)
IGH/MAFBDF-XL t(14;20)
IGH/MAFDF- XL t(14;16)
CCND3/IGHDF-XL t(6;14)

From Meta systems Gm.

Chromosome analysis was carried out using automated slide scanner and Automated Karyotyping and FISH software from Applied Spectral Imaging Version 8.3.1 Israel.

RESULTS

A sample size of 70 individuals both retrospective and prospective data, were conducted out of which 45 were males and 25 were females. 16 female positive, 27 male positive and 27 were negative for MM.

We analyzed the gender distribution of the sample and found that males were predominant, with 45 out of 70 participants being male (64.3%). To test whether this was a statistically significant difference, we use dachi squared test with a significance level of 0.05. The test statistic was 5.14,

and the p-value was 0.023, indicating a significant association between gender and multiple myeloma, with males being more likely to develop the disease. (Fig. 1: Graph showing total sample size distribution)

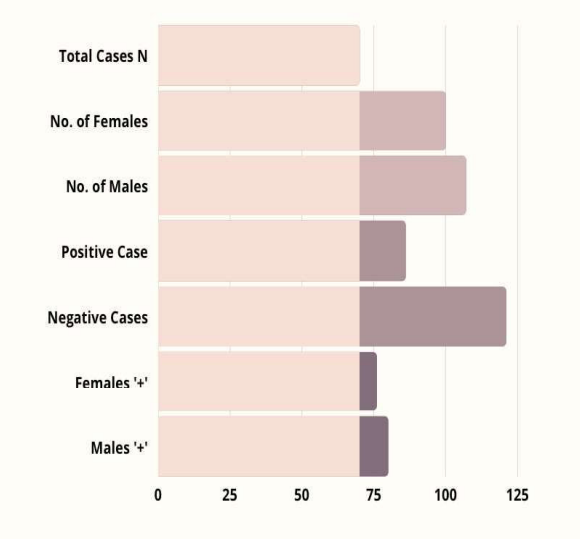

Fig. 1: Graph showing total sample size distribution)

Next, we examined the age distribution of the sample and found that individuals aged 60 or above were more likely to develop multiple myeloma.

To test whether this was a statistically significant difference, we used a one-sided z-test with a significance level of 0.05. The test statistic was 1.64, and the p-value was 0.051, which indicates that there is a marginally significant association between age above 60 and multiple myeloma.

In the present study, the chromosomal abnormalities included specific markers which were Monosomy 13, 13q deletion, IGH Breakapart and 17p deletion were seen in all the positive cases, In which, 17 cases showed positive for monosomy 13 with 13q del, 11 cases showed positive for IGH breakapart and 1 unique abnormality with monosomy 14 and 14 cases positive for P53 del.

DISCUSSION & CONCLUSION

Certain cytogenetic abnormalities are more common in older patients with multiple myeloma. According to a study published in the journal Leukemia, "older patients were more likely to have high-risk cytogenetic abnormalities, such as del(17p), t(4;14), and t(14;16)" (Boyd *et al*., 2018). In this present study 32 were above age of 60 years. (Fig. 2: Cells showing deletion for 13q)

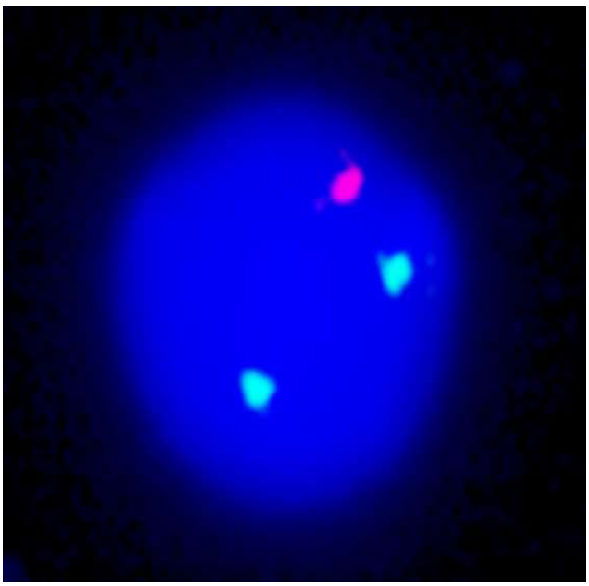

Fig. 2: FISH Image showing signals for deletion for 13q

Multiple myeloma is more common in men than women. According to a study published in the journal Cancer, "the incidence of multiple myeloma is higher in men than women, with a male-to-female ratio of approximately 1.5:1" (Kyle *et al*., 2007). Chromosomal abnormalities are more common in men with multiple myeloma. According to a study published in the journal Cancer," men with multiple myeloma were more likely to have chromosomal abnormalities, such as del (17p), t(4;14), and t(14;16), than women" (Kyle *et al*., 2007).

The results of the present study was suggestive of Male predominance in 64.4%. It is evident that the prognostic significance of cytogenetic abnormalities may differ between men and women with multiple myeloma (Gonzalez *et al*., 2019).

In conclusion, our study highlights the importance of cytogenetic analysis in diagnosing and managing multiple myeloma. The identification of specific chromosomal abnormalities can provide valuable information regarding disease prognosis and guide treatment decisions. Additionally, our findings suggest that male sex and advanced age are risk factors for multiple myeloma recurrence, but in the present study as the sample size was too small, statistically no appropriate conclusions can draw the inference.

Genetic counseling is an important part of the management of patients with multiple myeloma, particularly those with a family history of the disease or who have been identified as carriers of genetic mutations associated with increased risk. "Genetic counselling can also help patients and their

families cope with the emotional and psychological impact of a multiple myeloma diagnosis, as well as provide support for decision making regarding treatment and other aspects of care." (Giri *et al.*, 2017).

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