Original Article

Chromosomal Aberrations in Multiple Myeloma: A Study on Indian Population

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Abstract

Aims: The aim of this study was to evaluate the complexity of the chromosomal abnormalities in multiple myeloma (MM) cases and to correlate the findings with the previous reported cases. **Materials and Methods:** Bone marrow samples were obtained from patients with MM and sent for cytogenetic study. The patient's details were logged and the cytogenetic test was performed. The karyotypes were analyzed and interpreted as per the standard guidelines. **Results:** Of the compiled data of cases from 2013 to 2016, 34 patients were diagnosed with MM. About 15% were below the age of 50, maximum patients were between ages of 61 and 70 years (50%). There were 25 male and 9 female. Twenty-one cases had normal karyotypes and few cases showed structural rearrangements and numerical abnormalities. **Conclusions:** From the data compiled, only a total of 34 cases were positive for MM, indicating that the disease is quite rare in our population. It has been previously reported that the disease usually occurs in people over the age of 50 years, however, in this study, 5 (15%) were below the age of 50 indicating that MM can affect the age group below 50 years as well. The numerical, structural abnormalities and few clonal abnormalities observed in our study added a few more to the previously reported abnormalities. However, the interesting finding of our study was a case with a combination of clones of hypodiploidy, hyperdiploidy, hypotetraploidy, and hypertetraploidy which was in contrary to the reported literatures, which were only one type of ploidy were observed. Thus, the heterogeneity and complexity of the chromosomal abnormalities in MM and the challenge in staging the disease have been proven in our study.

Keywords: Chromosomal aberrations in multiple myeloma, cytogenetic markers in multiple myeloma, multiple myeloma

Introduction

Much has been studied regarding the biology and clinical implications of genetic abnormalities in multiple myeloma (MM). Conventional cytogenetics remains an important tool in elucidating the complex and diverse genetic anomalies of MM. Cytogenetics identifies two distinct groups of MM, hyperdiploid and nonhyperdiploid, and establishes the presence of prognostic chromosomal markers such as 13/13q, 17p, 8q24, and 16q aberrations. In most reported cases (50%–70%), the karyotype reveals normal metaphases that originate from the myeloid elements.[1,2] Even among patients with abnormal karyotypes, some of the important aberrations may be cryptic.[3,4] The cytogenetics information has also been thought to be reliable for the detection of chromosome 13 abnormalities including interstitial deletion and monosomy.[5,6] A few cases of MM karyotyped have pointed to the involvement of 1lq13, site of the BCLI proto-oncogene, or of 8q24, site of the MYC proto-oncogene. MM is characterized by the frequent occurrence of aneuploidy, and the prevalence of aneuploidy is independent of the stage. The most common trisomies are 3, 5, 6, 7, 9, 11, 15, 19, and 21, and the most common monosomies are 13, 8, 14, 16, 22, and X/Y.[7-11] Globally, aneuploidy analysis segregates patients into four subcategories as follows: hypodiploid, pseudodiploid, hyperdiploid, and near tetraploid (the last also referred to as the hypotetraploid) with hyperdiploidy being the most frequently occurring karyotype. Apart from the major chromosomal abnormalities of aneuploidy, translocation,

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and structural rearrangements such as deletion and duplication, some of the cases have also shown breakpoints at the loci of proto-oncogenes, tumor suppresser gene, or immunoglobulin-related gene especially involving 1p13, 11q13, 6q21, 7p11.2, 14q13, 17p11, and 19p13.3 regions.[12] The interpretation of cytogenetic results in MM is generally complicated due to the complexity of the chromosomal abnormalities and heterogeneity.[13]

Materials and Methods

Cytogenetics studies were done on either the bone marrow or the peripheral blood collected from patients with MM. The patient's details along with age, sex, and clinical details were logged. The samples were processed for overnight, 24 hrs, and 48 hrs culture, using RPMI-1640 medium (GIBCO-BRL) supplemented with 15% fetal bovine serum and antibiotics. The culture was arrested by using 50 µl of colcemid (10 µg/ml), the cells were then subjected to hypotonic treatment by adding 5 ml of 0.075 M potassium chloride with constant agitation on a vortex mixer. Freshly prepared fixative (methanol: acetic acid in the ratio of 3:1) was used. After two washes of fixative, slides were prepared from the pellet and GTG banded (trypsin and Giemsa stain). The slides were aged and subjected to trypsinization (10% trypsin) for 4–5 min, rinsed briefly in normal saline and stained with buffered Giemsa for 4–5 min followed by brief rinse in distilled water. Slides were then air-dried coverslipped and analyzed using spectral imaging software and were interpreted as per the standard guideline.

Results

Of the compiled data of cases from 2013 to 2016, 34 patients were diagnosed with MM. 5 (15%) were below the age of 50, maximum patients were between the ages of 61 and 70 years (17, i.e., 50%) [Table 1]. In our analysis of 34 cases, there were 25 males and 9 females [Table 2].

Of 34 patients diagnosed with MM, 21 cases had normal karyotypes, a few cases showed structural rearrangements such as deletions, duplication, addition, and translocations, a few cases showed numerical abnormalities of trisomy and monosomy, and a few cases showed hyperdiploidy and a few clonal abnormalities [Tables 2-4].

However, in contrary to the reported cases, our study showed a few other findings as well. One of the cases showed a combination of hypodiploidy, hyperdiploidy, hypotetraploidy, and hypertetraploidy [Figure 1], and three cases showed − Y[2], −X[1] indicating involvement of the sex chromosomes as well [Tables 2 and 3]. Earlier reports demonstrated that myeloma cells exhibit complex aberrations regardless of ploidy,[13] similar findings were noted in our study as well [Table 2 and Figure 2].

Discussion and Conclusion

Over the years, much has been learned about the chromosomal

Table 1: The age analysis of multiple myeloma patients

Age group (years)	Number of patients		Patients (%)
	Abnormal karyotype	Normal karyotype	
31-40	-	1	2.9
41-50	2	2	11.8
51-60	3	4	20.6
61-70	7	10	50.0
71-80	1	3	11.8
81-90	-	1	2.9

Table 2: Case details with age, sex, and karyotype

Serial number	Age/sex	Karyotype
1	65/male	46, XY (normal karyotype)
2	53/female	46, XX (normal karyotype)
3	68/female	46, XX (normal karyotype)
4	69/male	46, XY (normal karyotype)
5	74/male	46, XY (normal karyotype)
6	62/male	46, XY,+1, add (5q), +7, −8, +11, −13, −14, −21, +mar
7	42/male	46, XY (normal karyotype)
8	75/male	46, XY (normal karyotype)
9	69/female	Clones of hypodiploidy/diploidy/hyperdiploidy and predominantly hypotetraploidy and hypertetraploidy
10	78/female	46, XX/hypodiploidy and clones of endoreduplication
11	63/male	Hypodiploidy/46, XY,+3,?del17(p),−18/46, XY
12	60/male	46, XY[9]/45, XY, del (4)(p15.1),−21[4]/46, XY, del (4)(p15.1)[1] Hypodiploidy[5]
13	57/male	Hypodiploidy[8]/46, XY[3]/46, XY,−6, del(11)(q21), +15/45, XY[1]/45, XY, +15, −21, −22[1]/43, XY, +3, −9, −10, −20, −20, −22, +mar[1]/45, X,−Y/+mar[3]
14	62/male	46, XY (normal karyotype)
15	80/male	46, XY (normal karyotype)
16	62/female	46, X,−X, +1, add(1)(p13) x2,−2,+8,−13, der(16),?t(1;16)(q21;q22), +19, −21, −21, −22, +mar, +mar, +mar
17	55/male	49, XY, dup (1q), +3, +9, −13, +15, +21/49, XY, dup (1q), +3, +15, +21
18	65/female	46, XX (normal karyotype)
19	50/male	46, XY (normal karyotype)
20	65/male	46, XY (normal karyotype)
21	69/male	46, XY (normal karyotype)
22	52/male	46, XY (normal karyotype)
23	70/male	47, XY, del(1)(p31), del(13)(q14),−14,+16, der(16),?t(1;16)(q21;q22) x2,+20
24	55/female	46, XX (normal karyotype)
25	69/male	46, XY, del(6)(q22;q24)[3]/46, XY[5]
26	70/male	46, XY (normal karyotype)
27	65/male	46, XY (normal karyotype)
28	62/male	46, XY, dup(1q), t(8;11)(q24;q13), der(14q)
29	60/female	46, XX (normal karyotype)
30	47/male	46, XY [10]/46, XY, del (6)(q16;q23)[3]
31	34/female	46, XX (normal karyotype)
32	65/male	46, XY (normal karyotype)
33	48/male	46, X,−Y,+3
34	85/male	46, XY (normal karyotype)

aberrations and the heterogeneity that involves the cancer cells including those in MM.[14] MM reveals multiple numerical and structural chromosomal abnormalities. It is different from most other hematologic malignancies, which are typically less complex, and myeloma cytogenetically more resembles the complexity of solid tumors.[15]

In MM, it is usually seen that males are more commonly affected than females.[16,17] In our analysis of 34 samples, the same pattern was observed wherein 25 males and 9 females were affected. It is reported that the disease usually occurs in people over the age of 50 years, however, in our study of 34 cases, 5 (15%) were below the age of 50 indicating that the MM can also affect the age group below 50 years. The affected patients were most commonly between the age of 61 and 70, i.e., 17 (50%), and 7/17 (41.2%) of the cases among this age group of 61–70 years had abnormal karyotype.

It has been reported that hyperdiploidy of chromosomes 3, 5, 7, 9, 11, 15, 19, and 21 was observed in MM [10] and is generally associated with a good prognosis.[18] In this study, in addition to the above, hyperdiploidy involving a few other chromosomes such as 1, 8, 18, and 20 were also observed. Many studies have shown that del(17p), t(4;14), t(14;16), del(12p), del(13q), 1q, and 11q abnormalities are considered as high-risk cytogenetic abnormalities and carry a poor prognosis.[19] Some of these abnormalities were observed in our study as well. Clones of endoreduplication along with hypodiploidy were seen in one of the cases. Endoreduplication (replication of the nuclear genome in the absence of cell division, which leads to elevated nuclear gene content and polyploidy) is known to correlate with aggressive evolution of MM.[20]

To the best of our knowledge and as per our literature search, only one type of ploidy has been observed in MM. However, in this study, case number 9 had a combination of ploidies, i.e., clones of hypodiploidy, hyperdiploidy, hypotetraploidy, and hypertetraploidy. This was a significant observation in our study. The most commonly reported monosomies are −8, −13, −14, −16, −22, and −X/Y[10-17] in addition to the above monosomies, our study recorded few other monosomies such as − 2, −6, −9, −10, −20, −21, and two of the cases showed −Y, and one case showed −X, that is, involvement of the sex chromosomes as well. Of 34 patients in our study, only a few cases showed structural abnormality, indicating that there were more of numerical abnormalities than structural abnormalities in MM.

Table 3: Types of chromosomal abnormalities observed in our study

Types of chromosomal abnormality	Types of chromosomal abnormalities observed in our study
Deletions	1p, 4p, 6q (two cases), 11q, 13q, and 17p
Duplications	1q
Addition	1p, 5q, 14q, and 16q (two cases)
Monosomy	−2, −6, −9, −10, −13 (three cases), −14, −20, −21, and −22
Trisomy	+1, +3 (four cases), +7, +8, +9, +11, +15, +18, +19, +20, +21
Translocations	t (1;16)(q21;q22) (two cases), t (8;11)(q24;q13)
Y	−Y (two cases)
X	−X (one case)
Mar	Unknown segment

Table 4: Comparison of previously reported chromosomal abnormalities in multiple myeloma and chromosomal abnormalities observed in our study

Previously reported chromosomal abnormalities in MM	Chromosomal abnormalities observed in our study
Normal karyotype	21 cases
t(14;20)	-
t(4;14)	del (4)(p15.1) (one case)
t(14;16)	-
t(11;14)	-
del(17p)	One case
del(12p)	-
del(13q)	Chr 13 abnormalities (four cases)
1q abnormality	Chr 1 abnormalities (four cases)
11q abnormality	Two cases
Monosomy of−2, −6, −9, −10, −13, −14, −20, −21, −22	✓
Hyperdiploidy involving+1, +3, +7, +8, +9, +11, +15, +18, +19, +20, and +21	✓
Hypodiploidy	✓
Hypotetraploidy	✓
Chr 6 abnormalities	Three cases
Hypodiploidy and clones of Endoreduplication	One case
-	Combination of hypodiploidy/hyperdiploidy/hypotetraploidy/ hypertetraploidy (1 case)
−X/−Y	−X (one case), −Y (two cases)

MM: Multiple myeloma

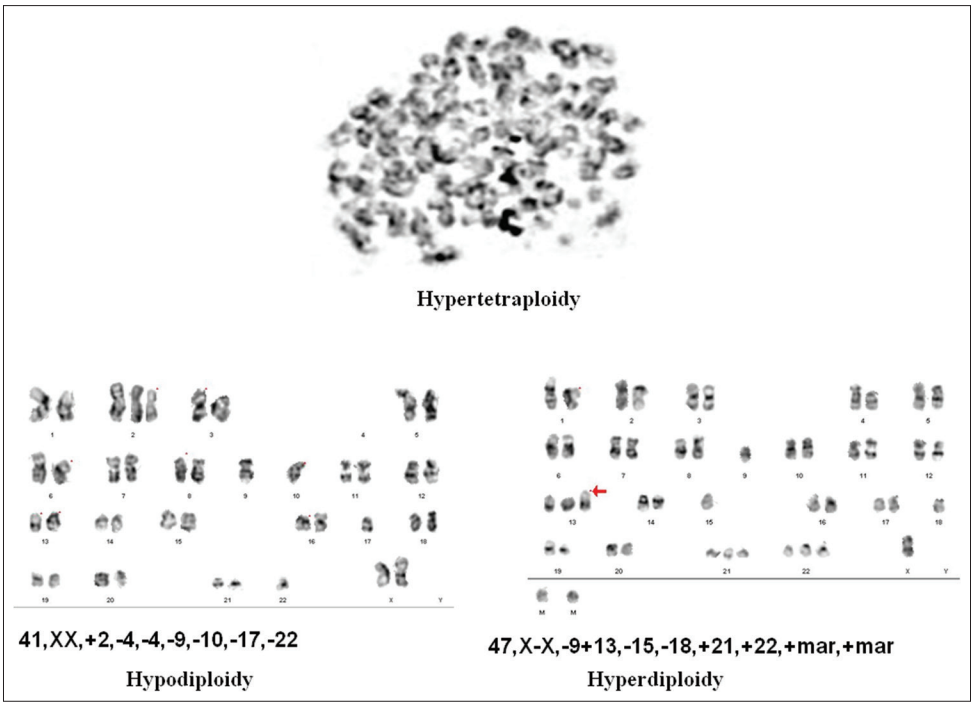

Figure 1: Case 9 with clones of hypertetraploidy, hypodiploidy, and hyperdiploidy

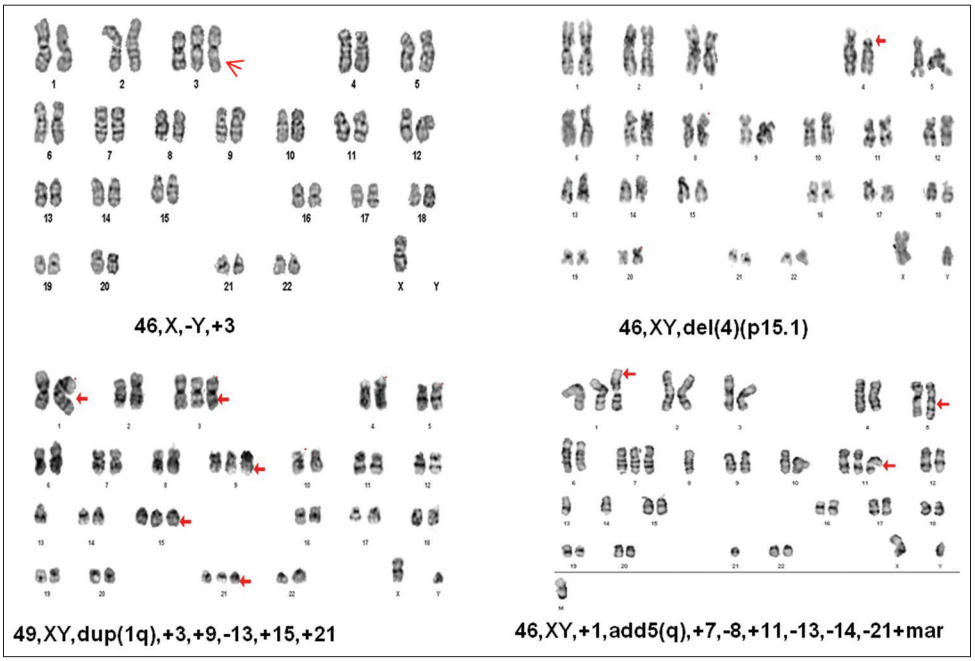

Figure 2: Few cases of multiple myeloma showing the complexity of the chromosomal abnormalities

Thus, MM is a plasma cell malignancy characterized by marked epidemiological, biological, and clinical heterogeneity with a lot of variation in the chromosomal number and structural abnormalities. The numerical abnormalities, structural abnormalities, and a few clonal abnormalities observed in our study added a few more to the previously reported abnormalities, and the study thus proves the numerical and structural complexity of the chromosomes in MM. This study also ascertains that the interpretation of cytogenetic results in MM is quite complicated due to the complexity of the chromosomal abnormalities, and the staging of the disease is also a challenge. However, since cytogenetics tests for MM are not very frequently referred and the frequency of cytogenetics abnormalities in MM is low, therefore, a prolonged study with a larger number of cases would be required to enable us to draw statistically significant conclusions.

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Conflicts of interest

There are no conflicts of interest.

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