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Conventional Cytogenetic Abnormalities in Plasma Cell Myeloma and Their Prognostic Effect: A Single Center Experience in the Middle East

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Abstract

Background: Given the prognostic importance of cytogenetic aberrations in plasma cell neoplasms, the present retrospective study was conducted to analyze cytogenetic abnormalities in plasma cell myeloma cases in a single center in the Middle East.

Method: In this retrospective cross-sectional study, we selected 42 patients referred to the molecular and cytogenetic department from 2013 to 2016 for initial assessment by immunohistochemical, flow cytometric, and cytogenetic studies. Chromosomal analysis was performed after a 72-hour unsynchronized culture and Giemsa banding; the result was reported according to ISCN 2016.

Results: 32.5% of the patients showed an abnormal karyotype, of whom 53.8% were hyperdiploid and the rest were assigned to the non-hyperdiploid group. The gain of 1q and monosomy 13/ deletion 13q were the most common structural abnormalities accounting for 38.4% and 30.7%, respectively. t(11;14) was the only detected 14q32 rearrangement observed in 15.4% of the cases. The mean survival time in normal, hyperdiploid, and non-hyperdiploid groups was 29.5±1.7, 16.6±2.9 and 6.1±2.1 months, respectively.

Conclusion: Cytogenetic abnormalities of plasma cell myeloma in this center were relatively similar to previous reports in the literature; moreover, hyperdiploidy was the most common cytogenetic aberration. As no cryptic aberration could be identified, we recommend the use of more precise techniques such as FISH in addition to conventional G banding to detect cryptic aberrations. Survival of the non-hyperdiploid group was the worst.

Keywords: Multiple myeloma, Cytogenetics, Chromosomal aberrations

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Introduction

A plasma cell neoplasm is characterized by the accumulation of monoclonal plasma cells in the bone marrow. This malignancy is a clinico-pathologic spectrum. It ranges from a premalignant stage called monoclonal gammopathy of unknown significance to symptomatic plasma cell myeloma (multiple myeloma) with symptoms such as bone destruction, renal failure, and bone marrow suppression.[1,2]

During disease progression, plasma cell proliferation occurs in a series of phases, including a non-proliferative phase, an active phase with certain proliferating cells, and a fulminant phase with an increase in plasma blasts. Approximately, one-third of patients with active myeloma have an abnormal karyotype.[3]

The conventional cytogenetic study should be considered as an initial diagnostic work-up in plasma cell myeloma due to its prognostic information. Cytogenetic classification of plasma cell neoplasms can result in better risk stratification and the selection of a proper therapeutic strategy. Based on risk stratification, this neoplasm was simply categorized into two subtypes, namely non-hyperdiploid and hyperdiploid. The former is associated with a worse prognosis compared with the latter.[4-7] Therefore, this study was designed to evaluate cytogenetic abnormalities in patients with plasma cell myeloma as an initial assessment in a single center in Iran.

Materials and Methods

This retrospective cross-sectional study included the patients referred to the molecular pathology department with clinical impression of plasma cell myeloma and the cases with clinical and laboratory evidence of significant monoclonal plasma cell proliferation (such as clinical evidence of end-organ damages and/or M-components higher than 3g/dl and/or light chain restriction) between the years 2013 and 2016 following the approval of the Institutional Review Board and obtaining informed consent. The patients with polyclonal plasma cell proliferation and/or bone marrow involvement by other malignancies were excluded. Ultimately, 42 out of the 47 subjects were selected retrospectively. They were referred

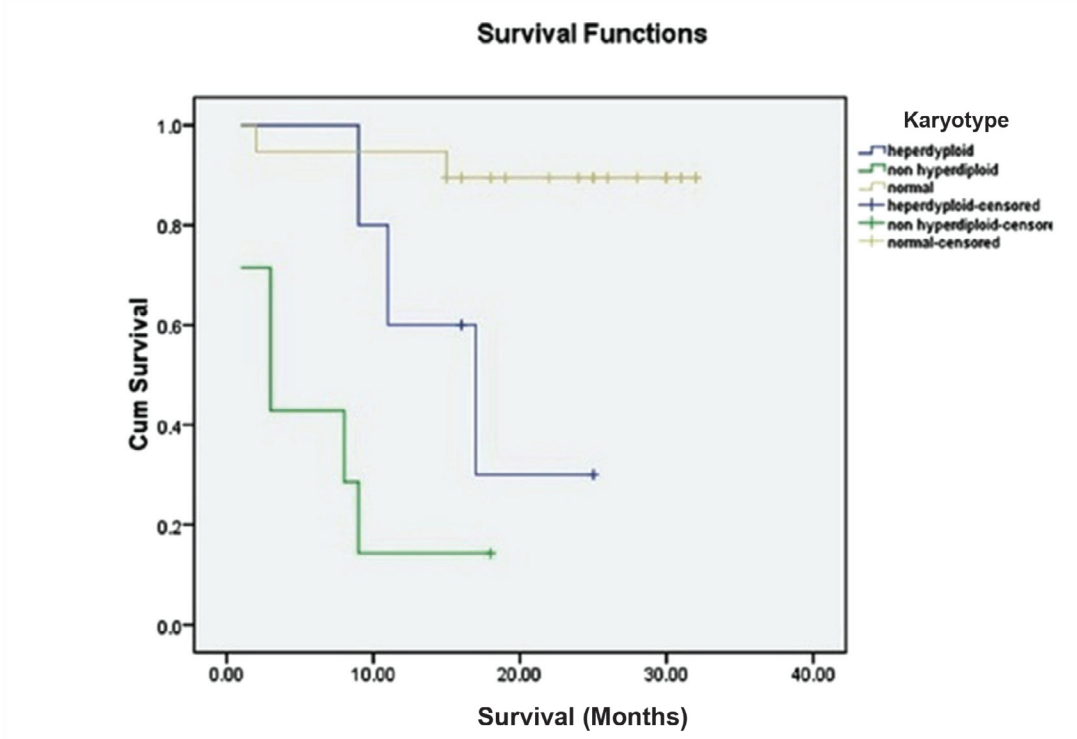

Figure 1. Kaplan Meier analysis showed a shorter survival in cases with abnormal karyotype. However, hyperdiploid cases had a better survival in comparison with non-hyperdiploid cases.
Cum survival= Cumulative survival

Table 1. Demographic, survival, hematopathological, and cytogenetic features of the patients with plasma cell myeloma who had abnormal conventional karyotype

Patient ID	Age	Sex	Percent of plasma cells	Type of light chain restriction	Karyotype abnormality category	Survival
Case 1	79 years	male	30%	kappa monotypic	non-hyperdiploid	9 months
Case 2	78 years	male	80%	kappa monotypic	non-hyperdiploid	3 months
Case 3	53 years	male	70%	kappa monotypic	non- hyperdiploid	3 months
Case 4	59 years	female	70%	kappa monotypic	hyperdiploid	17 months
Case 5	61 years	female	5%	lambda monotypic	hyprerdiploid	11 months
Case 6	61 years	male	25%	lambda monotypic	hyperdiploid	1 month
Case 7	54 years	male	65%	kappa monotypic	hyperdiploid	16 months
Case 8	40 years	male	50%	kappa monotypic	hyperdiploid	25 months
Case 9	48 years	female	28%	lambda monotytic	hyperdiploid	9 months
Case10	44 years	male	25%	lambda monotypic	hyperdiploid	undetermined
Case11	44 years	female	7%*	kappa monotypic	non-hyperdiploid	18 months
Case12	60 years	male	90%	lambda monotypic	non-hyperdiploid	1 months
Case13	69 years	female	30%	kappa monotypic	non-hyperdiploid	3 months

Patient ID	Karyotype ISCN result
Case 1	42,XY,-8,der(9)t(1;9)(q10;q34),-13,der(16)t(1;16)(q12;q24),del(17)(q12),der(19)t(1;19)(q21;p13),-21,-22[7]/46,XY[11]
Case 2	45,X,-Y[9]/45,X,-Y,t(11;14)(q13;q32)[6]
Case 3	46,XY,t(11;14)(q13;q32)[4]/46,XY[15]
Case 4	48,X,-X,+5,+7,+9,+15,-13[4]/48,X,-X,+5,+7,+9,+19,-13[3]/47,X,-X,+5,+7,+9,+15,-13,-16[4]/46,XX[16]
Case 5	50,XX,+1,der(1;15)(q10;q10),+3,+6,del(6)(p22),+8,+19[7]/46,XX[9]
Case 6	54,XY,+1,+4,+5,+6,-9,+11,+15,+19,+21,+22[9]/46,XY[11]
Case 7	54,XY,+3,+5,+5,del(6)(q16q22),+7,+9,+11,+15,-16,+19,+21[7]/46,XY[10]
Case 8	57,XY,+1,+1,del(1)(p13)×2,+3,+5,+7,-8,+9,+9,+11,+15,+17,+19,+21[6]/46,XY[11]
Case 9	58,XX,+1,der(2)t(1;2)(p35,q21),+3,+6,t(6;9)(q21;q12),+11,-13,+15,+17,+18,+18,+18,+19,+20,+mar[6]/46,XX[12]
Case 10	59,X,-Y,+2,+3,+4,+5,+7,+7,+9,+13,+15,+16,+19,+19,+20,+21[5]/59,X,-Y,+2,+3,+4,+5,+7,+7,ins(7;12)(q36;q13q20),+9,+13,+15,+16,+19,+19,+20,+21[2]/59,X,-Y,+2,+3,+4,+5,+7,+7,ins(7;12)(q36;q13q20),+9,+13,add(13)(q12),+15,+16,+19,+19,+20,+21[2]/59,X,-Y,+2,+3,+4,+5,+7,+7,ins(7;12)(q36;q13q20),+9,dup(12)(q13),+13, add(13)(q12),+15,+16,+19,+19,+20,+21[3]/46,XY[8]
Case 11	82~84,XXXX,-2,-2,-4,-4,-5,-6,-6,-8,+10,+11,+11,+12,-13,-13,-14,-14,-15,-15,+16,+16,+17,-18,-18,-19,+20,+20[3]/46,XX[12]
Case12	84~86,XY,-X,-Y,del(1)(p13),i(1)(q10),+2,-5,-5,-8,-9,-10,+11,-13,-14,+15,-16,+17,+17,+18,-19,-20,-21[4]/46,XY[11]
Case 13	102,XXYY,+X,+X,+1,+2,+3,+3,+3,+4,-5,-5,-5,-5,+6,+6,-7,-8,-8,-9,-9,-10,+12,+12,+12,+12,-13,+15,-17,-17,+18,+21,+21,+21,+22,+22,+22,+22[4]/46,XY[11]

add= addition, del= deletion, der= derivative, dup= duplication, i= isochromosome, ins= insertion, mar= marker chromosome, t= translocation; ¶ This patient had an M component of 5g/dL and vertebral bone lesions in MRI.; * This patient had anemia and an M component of 6g/dL

for immunohistochemical, flow cytometric, and cytogenetic study. Percentage of plasma cells was reported according to bone marrow aspiration differential count or flow cytometry of bone marrow aspirate. Type of light chain restriction was determined via immunohistochemistry and flow cytometry by use of following markers: CD38, CD138, kappa, lambda, CD56, and CD19.

For cytogenetic evaluation, a 72-hour unsynchronized culture was performed with the following steps: adding 1 mL of bone marrow to 10 mL of complete RPMI and incubating at 37°C for 72 hours, harvesting through the addition of 10 µg/mL colcemid, and finally the addition of hypotonic solution and Carnoy's fixative. Six slides were prepared by Giemsa staining for each case.[8] A minimum of 15 metaphases were analyzed. The final results were reported according to the International System for Human Cytogenetic Nomenclature (ISCN) 2016.[9] The results were stratified into normal diploid group (46 chromosomes without any numerical or structural abnormality), hyperdiploid group (48-75 chromosomes), and non-hyperdiploid group. The latter was further categorized into hypodiploid (less than 48 chromosomes), pseudodiploid (46 chromosomes but with structural abnormalities), and near-tetraploid subgroups (>75 chromosomes).

Statistical analysis was done using SPSS

software version 16. Chi-square and ANOVA test were used where appropriate. Survival analysis was done by Kaplan Meier test. A *P*-value < 0.05 was considered as statistically significant.

Results

42 patients were included in this study; however, two patients' bone marrow samples failed to grow in culture media and led to no metaphase cells (a failure rate of 4.7%). Out of 40 patients, 26 (65%) were men, 14(35%) were women, and the gender ratio was 1.85:1(M:F). Subjects' median age was 62±12.6 years. Median plasma cell percentage was 39±21.2%. Light chain restriction was detected in 36 patients. 22 were kappa monotypic (55%), 14 were lambda monotypic (35%), and the rest were undetermined (10%).

The cytogenetic study revealed that 13 subjects had abnormal karyotypes (32.5%), of which seven patients had hyperdiploidy (17.5%), and six had non-hyperdiploidy (15%). Table 1 shows the demographic, survival, hematopathologic, and cytogenetic characteristics of these patients. A normal karyotype was observed in 27 subjects (67.5%).

There was no statistically significant relationship between karyotype abnormalities and age, sex, percentage of marrow plasma cells, and light chain restriction. The percentage of bone marrow plasma cells was 47.8±19, 47.4±37.5, and 34.8±17.9 in hyperdiploid, non-hyperdiploid, and normal diploid groups, respectively. Although it seemed to be 13% higher in the cytogenetically abnormal group, their difference did not reach a statistically significant level.

Kaplan Meier analysis during the three-year follow-up revealed a mean survival time of 29.5±1.7, 16.6±2.9 and 6.1±2.1 months in normal, hyperdiploid, and non-hyperdiploid groups, respectively. This difference was statistically significant (P<0.001), indicating that in the abnormal group, hyperdiploid patients had a better prognosis (Figure 1).

Karyotype analysis results revealed that numeric chromosome gain was a common finding.

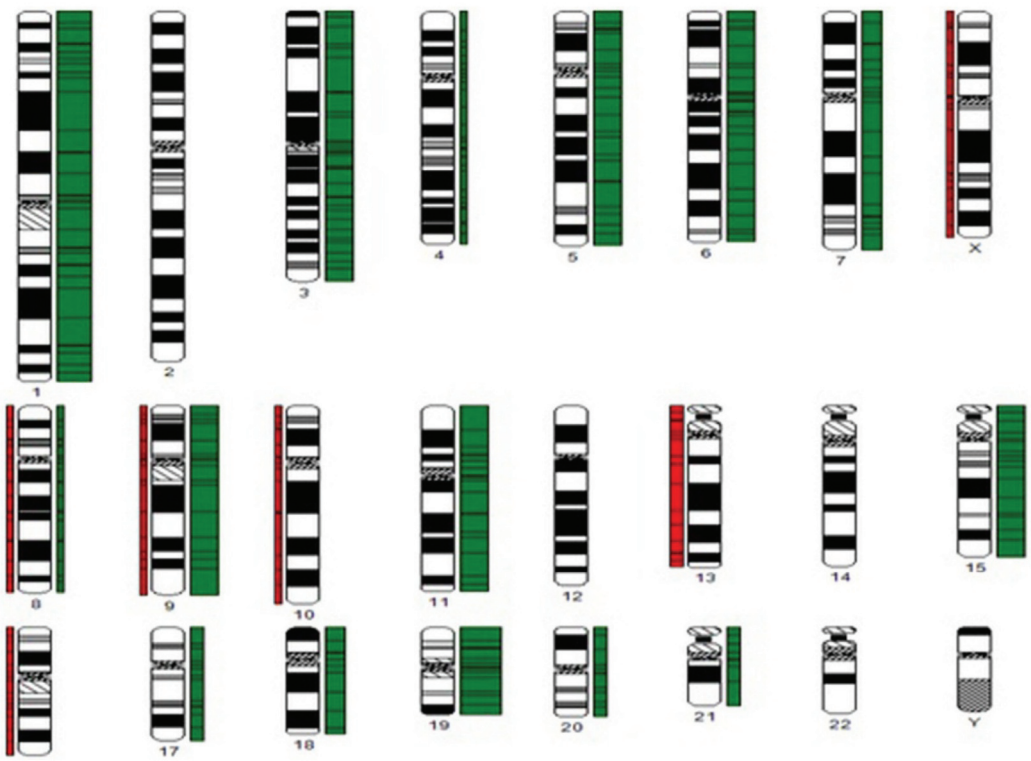

Figure 2. Cydas online software analysis of hyperdiploid cases revealed that the gain of chromosome 19 and loss of chromosome 13 were the most common numerical gain and loss, respectively (chromosome gains are shown as green bars on the right and chromosome losses are shown as red bars on the left).

Table 2. Frequencies of chromosomal structural aberrations in plasma cell myeloma patients with abnormal karyotype

Cytogenetic abnormalities	Frequency	Percent
1q gain	5/13	38.4%
-13/del 13q	4/13	30.7%
t(11;14)(q13;q32)	2/13	15.3%
del(1)(p13)	2/13	15.3%
add(13)(q12)	1/13	7.6%
del(6)(p22)	1/13	7.6%
del(6)(q16q22)	1/13	7.6%
del(17)(q21)	1/13	7.6%
dup(12)(q13)	1/13	7.6%
ins(7;12)(q36;q13q20)	1/13	7.6%
t(6;9)(q21;q12)	1/13	7.6%

add= addition, del= deletion, der= derivative, dup= duplication, ins= insertion, t= translocation.

The gain of chromosomes 19 was the most prevalent among hyperdiploid group followed by chromosomes 1, 15, 11, and 3. Loss of chromosomes 13 and 8 were the most common monosomies (Figures 2 and 3).

The gain of chromosome 1q was the most frequent chromosomal structural abnormality observed in five out of 13 abnormal karyotypes (38.4%). Monosomy 13/ deletion of 13q was the second most common structural abnormality occurring in four of 13 abnormal karyotypes (30.7%). t(11;14) and deletion of 1p were both the third common chromosomal structural abnormalities with a frequency of 15.3%. Concomitant monosomy 13/ deletion 13q was detected in two out of five patients with a gain of 1q (40%). Other abnormalities were not recurrent and were occasionally observed (Table 2).

Discussion

This retrospective study showed that there was a male predominance in plasma cell myeloma cases and more frequent kappa restriction among plasma cell neoplasms. Furthermore, no significant association existed between light chain restriction and dismal cytogenetic abnormalities. Hyperdiploidy was the most common numerical abnormality. The gain of chromosome 1q, monosomy 13/ deletion of 13q, rearrangement of 14q32 and deletion of 1p were detected as recurrent structural abnormalities. The relationship between the gain of 1q and the monosomy of 13/ deletion of 13q was another finding.

This study also revealed that 32.5% of plasma cell myeloma cases had a cytogenetic abnormality in the conventional karyotype. Hyperdiploidy accounted for 53.8% of all abnormal karyotypes, and the remaining 46.2% were non-hyperdiploid. The results of this study were consistent with previous surveys. According to the literature review, abnormal karyotypes were found in 30-50% of cases by conventional cytogenetic banding. However, a wide range of genetic alterations (from 15% to 75 %) were reported.[10-14] In a similar survey on 84 multiple myeloma patients in France, 54% were hyperdiploid and the remaining 46% were non-hyperdiploid.[15] In a recent study on 222 multiple myeloma cases in Korea, clonal chromosomal abnormalities were slightly higher than our study, reaching 45%.[16] These different detection rates could be attributed to various stages of the disease, tumor heterogenicity, and different cell culture techniques. More precise techniques such as fluorescence in situ hybridization (FISH) and molecular genetic studies can detect higher genetic alterations such as cryptic changes like t(4;14)(p16;q32).[1,2] Similarly, in a recent study on 45 subjects in Singapore, 20 of 35 multiple myeloma cases were hyperdiploid (57.1%) and the remaining 15 subjects were non-hyperdiploid (42.9%).[6] In literature, 55-60% of multiple myeloma patients had hyperdiploidy with a gain of odd chromosomes.[17] Hyperdiploid group had a better overall survival in comparison with the non-hyperdiploid group, which might be due to the dosage impact of genes on drug sensitivity or tumor suppression.[18-19]

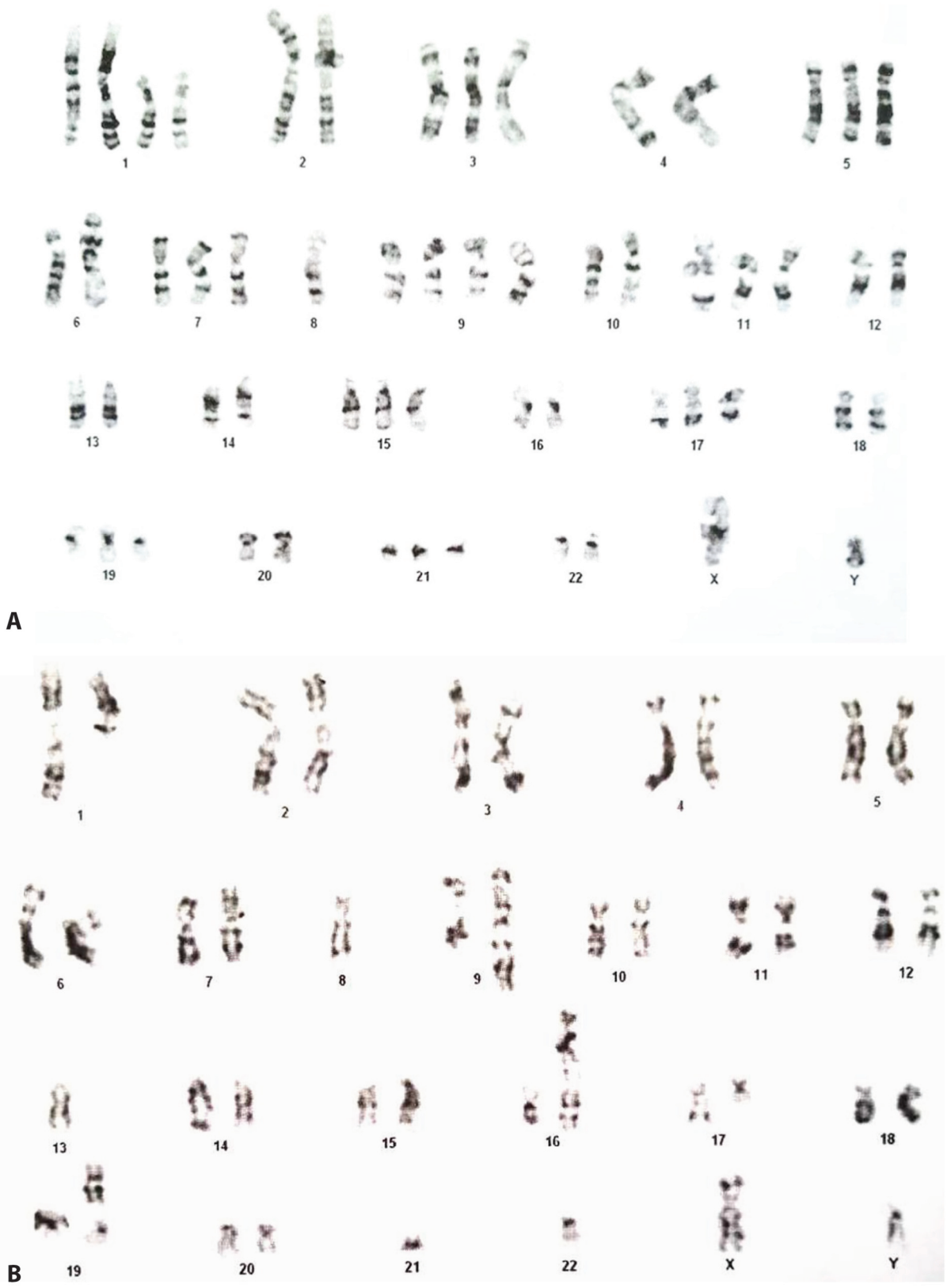

Figure 3. A. Hyperdiploidy in plasma cell myeloma with the gain of odd number chromosomes and 1p deletion (ISCN result: 57,XY,+1,+1,del(1)(p13) ×2,+3,+5,+7,-8,+9,+9,+11,+15,+17,+19,+21); B. Hypodiploidy in plasma cell myeloma with monosomy 13, 21, 22, and deletion of chromosome 17 long arm. Unbalanced translocation of chromosome 1q to chromosomes 9,16, and 19 was another finding which resulted in 1q gain (ISCN result: 42,XY,-8,der(9)t(1;9)(q10;q34),-13,der(16)t(1;16)(q12;q24),del(17)(q12),der(19) t(1;19)(q21;p13),-21,-22).

Among chromosomal structural abnormalities, chromosome 1 aberrations were the most common. Unbalanced translocation of 1q was commonly observed. This type of translocation led to 1q amplification and increased expression of genes such as CKS1B, ANP32E, PDZK1, and BCL9.[20-22] In this study, chromosomes 15, 16, and 19 were receptor chromosomes for 1q. Isochromosome 1q was another pattern of 1q gain observed in one patient. Gain of 1q was associated with short-term survival.[20] Even hyperdiploid cases with this structural abnormality had more aggressive disease courses with a worse prognosis.[23-24] In the present study, only one hyperdiploid case had concomitant 1q gain and a nine-month survival, which was obviously shorter than pure hyperdiploid cases. Noteworthy, the type of therapy was not known for any of the cases, which could have a cofounding impact on the survival analysis. An interesting finding during the analysis of cases with 1q gain was the concomitant monosomy 13/ del 13q in two out of five patients (40% of them), which was a small cohort. Monosomy 13 or deletion of 13q was the second most common abnormality detected in 30.7% of cases in the current. Some of the previous studies considered monosomy 13/ deletion 13q as the most frequent abnormality.[13,25-26] However, recent studies by FISH technique found that 1q abnormalities were more prevalent.[27-28]

The next common abnormality in this study was 14q32 rearrangements happening in 15.4% of cases with abnormal karyotype. Translocations of 14q32 can occur with chromosomes 4, 6, 11, 16, and 20. In our study, two cases had t(11;14)(q13;q32). This type of translocation usually takes place in the early stage of multiple myeloma; its frequency is approximately 15% among multiple myeloma cases. This type of translocation entails cyclin D1 up-regulation and B lymphoid immunophenotype. One of the cases with this translocation had an apparent lymphoplasmacytoic morphology which was immunohistochemically positive for CD38, CD138, kappa, CD20, and cyclin D1 (in favor of plasma cell myeloma with lymphoplasmacytic morphology) but negative for lambda and CD19 (against lymphoplasmacytic lymphoma).[13,22,27-31] As some translocations with 14q32 rearrangements are cryptic and small, these types of translocations other than t(11;14)(q11;q32) were not diagnosed in this study that used G banding technique with a low resolution. This fact necessitates the usage of more precise methods, such as FISH in addition to conventional G banding in plasma cell myeloma cytogenetic study.

One of the limitations of this study was the lack of FISH analysis to detect cryptic changes due to low financial resources. The other limitation was the absence of thorough clinical information to correlate with laboratory findings.

In conclusion, cytogenetic abnormalities in this center were in line with previous reports in the literature. However, some aberrations such as cryptic abnormalities could not be detected by conventional chromosome banding. Thus, the application of more precise methods such as FISH is recommended in addition to conventional cytogenetic studies. The survival of the non-hyperdiploid group was the worst.

Acknowledgment

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Conflict of Interest

None declared.

References

1. Rajkumar SV. Multiple myeloma: 2014 Update on diagnosis, risk-stratification, and management. *Am J Hematol*. 2014;89(10):999-1009. doi:10.1002/ajh.23810
2. Talley PJ, Chantry AD, Buckle CH. Genetics in myeloma: genetic technologies and their application to screening approaches in myeloma. *Br Med Bull.* 2015;113(1):15-30. doi:10.1093/bmb/ldu041.
3. Sawyer JR, Waldron JA, Jagannath S, Barlogie B. Cytogenetic findings in 200 patients with multiple myeloma. *Cancer Genet Cytogenet.* 1995;82(1):41-9. doi:10.1016/0165-4608(94)00284-i.

4. Smadja NV, Bastard C, Brigaudeau C, Leroux D, Fruchart C; Groupe Français de Cytogénétique Hématologique. Hypodiploidy is a major prognostic factor in multiple myeloma. *Blood*. 2001;98(7):2229-38. doi:10.1182/blood.v98.7.2229.
5. Shaughnessy J, Jacobson J, Sawyer J, McCoy J, Fassas A, Zhan F, et al. Continuous absence of metaphase-defined cytogenetic abnormalities, especially of chromosome 13 and hypodiploidy, ensures long-term survival in multiple myeloma treated with total therapy I: interpretation in the context of global gene expression. *Blood.* 2003;101(10):3849-56. doi: 10.1182/blood-2002-09-2873.
6. Lim AS, Krishnan S, Lim TH, See K, Ng YJ, Tan YM, et al. Amplification of 1q21 and other abnormalities in multiple myeloma patients from a tertiary hospital in Singapore. *Indian J Hematol Blood Transfus.* 2014;30(4):253-8. doi: 10.1007/s12288-013-0294-8.
7. Debes-Marun CS, Dewald GW, Bryant S, Picken E, Santana-Davila R, Gonzalez-Paz N, et al. Chromosome abnormalities clustering and its implications for pathogenesis and prognosis in myeloma. *Leukemia.* 2003: 17(2):427-36. doi: 10.1038/sj.leu.2402797.
8. Swansbury,J. Cancer cytognetics-methods and protocols. Totowa: Humana Press; 2003.
9. McGowan-Jordan J, Simson A, Schmid M. ISCN 2016: An international system for human cytogenomic nomenclature (2016). Basel: Karger; 2016.
10. Sawyer JR. The prognostic significance of cytogenetics and molecular profiling in multiple myeloma. *Cancer Genet.* 2011;204(1):3-12. doi: 10.1016/j.cancergencyto.2010.11.002
11. Lai YY, Huang XJ, Cai Z, Cao XS, Chen FP, Chen XQ, et al. Prognostic power of abnormal cytogenetics for multiple myeloma: a multicenter study in China. *Chin Med J.* 2012;125(15):2663-70.
12. Tiong LA, Hui LT, Shien SK, Jun NU, Min TY, Lian CN, et al. Cytogenetic and molecular aberrations of multiple myeloma patients: a single centre study in Singapore. *Chin Med J.* 2013;126(10):1872-7. doi: 10.3760/cma.j.issn.0366-6999.20123344.
13. Jekarl DW, Min CK, Kwon A, Kim H, Chae H, Kim M, et al. Impact of genetic abnormalities on the prognoses and clinical parameters of patients with multiple myeloma. *Ann Lab Med*. 2013;33(4):248-54. doi: 10.3343/alm.2013.33.4.248.
14. Waheed S, Shaughnessy JD, van Rhee F, Alsayed Y, Nair B, Anaissie E, et al. International staging system and metaphase cytogenetic abnormalities in the era of gene expression profiling data in multiple myeloma treated with total therapy 2 and 3 protocols. *Cancer.* 2001;117(5):1001-9. doi: 10.1002/cncr.25535.
15. Smadja NV, Fruchart C, Isnard F, Louvet C, Dutel JL, Cheron N, et al. Chromosomal analysis in multiple myeloma: cytogenetic evidence of two different diseases. *Leukemia.* 1998;12(6):960-9. doi: 10.1038/sj.leu.2401041.
16. Li S, Lim HH, Woo KS, Kim SH, Han JY. A retrospective analysis of cytogenetic alterations in patients with newly diagnosed multiple myeloma: a single center study in Korea. *Blood Res.* 2016;51(2):122-6. doi: 10.5045/br.2016.51.2.122.
17. Chng WJ, Glebov O, Bergsagel PL, Kuehl WM. Genetic events in the pathogenesis of multiple myeloma. *Best Pract Res Clin Haematol*. 2007;20(4):571-96. doi: 10.1016/j.beha.2007.08.004.
18. Avet-Loiseau H, Attal M, Campion L, Caillot D, Hulin C, Marit G, et al. Long-term analysis of the IFM 99 trials for myeloma: cytogenetic abnormalities [t (4;14), del (17p), 1q gains] play a major role in defining long-term survival. *J Clin Oncol.* 2012;30(16):1949-52. doi: 10.1200/JCO.2011.36.5726.
19. Kumar S, Fonseca R, Ketterling RP, Dispenzieri A, Lacy MQ, Gertz MA, et al. Trisomies in multiple myeloma: impact on survival in patients with high-risk cytogenetics. *Blood.* 2012;119(9):2100-5. doi: 10.1182/blood-2011-11-390658.
20. Shaughnessy JD, Zhan F, Burington BE, Huang Y, Colla S, Hanamura I, et al. A validated gene expression model of high-risk multiple myeloma is defined by deregulated expression of genes mapping to chromosome 1. *Blood.* 2007: 109(6):2276-84. doi: 10.1182/blood-2006-07-038430.
21. Sawyer JR, Tricot G, Lukacs JL, Binz RL, Tian E, Barlogie B, et al. Genomic instability in multiple myeloma: evidence for jumping segmental duplications of chromosome arm 1q. *Genes Chromosomes Cancer*. 2005;42(1):95-106. doi: 10.1002/gcc.20109.
22. Hanamura I, Stewart JP, Huang Y, Zhan F, Santra M, Sawyer JR, et al. Frequent gain of chromosome band 1q21 in plasma-cell dyscrasias detected by fluorescence in situ hybridization: incidence increases from MGUS to relapsed myeloma and is related to prognosis and disease progression following tandem stem-cell transplantation. *Blood.* 2006;108(5):1724-32. doi: 10.1182/blood-2006-03-009910.
23. Carrasco DR, Tonon G, Huang Y, Zhang Y, Sinha R, Feng B, et al. High-resolution genomic profiles define distinct clinico-pathogenetic subgroups of multiple myeloma patients. *Cancer Cell.* 2006;9(4):313-25. doi: 10.1016/j.ccr.2006.03.019.
24. Chng WJ, Santana-Davila R, Van Wier SA, Ahmann GJ, Jalal SM, Bergsagel PL, et al. Prognostic factors for hyperdiploid-myeloma: effects of chromosome 13 deletions and IgH translocations. *Leukemia.* 2006;20(5):807. doi: 10.1038/sj.leu.2404172.
25. Lim JH, Seo EJ, Park CJ, Jang S, Chi HS, Suh C, et al. Cytogenetic classification in Korean multiple myeloma patients: prognostic significance of hyperdiploidy with 47-50 chromosomes and the number of structural abnormalities. *Eur J Haematol.*

2014;92(4):313-20. doi: 10.1111/ejh.12257.
26. Jimenez-Zepeda VH, Neme-Yunes Y, Braggio E. Chromosome abnormalities defined by conventional cytogenetics in plasma cell leukemia: what have we learned about its biology? *Eur J Haematol.* 2011;87(1):20-7. doi: 10.1016/j.cancergencyto.2004.05.004.
27. Oh S, Koo DH, Kwon MJ, Kim K, Suh C, Min CK, et al. Chromosome 13 deletion and hypodiploidy on conventional cytogenetics are robust prognostic factors in Korean multiple myeloma patients: web-based multicenter registry study. *Ann Hematol*. 2014;93(8):1353-61. doi: 10.1007/s00277-014-2057-5.
28. Caltagirone S, Ruggeri M, Aschero S, Gilestro M, Oddolo D, Gay F, et al. Chromosome 1abnormalities in elderly patients with newly diagnosed multiple myeloma treated with novel therapies. *Haematologica.* 2014;99:1611-7. doi: 10.3324/ haematol.2014.103853.
29. An G, Xu Y, Shi L, Shizhen Z, Deng S, Xie Z, et al. Chromosome 1q21 gains confer inferior outcomes in multiple myeloma treated with bortezomib but copy number variation andpercentage of plasma cells involved have no additional prognostic value. *Haematologica*. 2014;99(2):353-9. doi: 10.3324/ haematol.2013.088211.
30. Jimenez-Zepeda VH, Braggio E, Fonseca R. Dissecting karyotypic patterns in non-hyperdiploid multiple myeloma: an overview on the karyotypic evolution. *Clin Lymphoma Myeloma Leuk.* 2013;13(5):552-8. doi: 10.1016/j.clml.2013.05.005.
31. Fonseca R, Blood EA, Oken MM, Kyle RA, Dewald GW, Bailey RJ, et al. Myeloma and the t (11; 14)(q13; q32); evidence for a biologically defined unique subset of patients. *Blood.* 2002;99(10):3735-41. doi: 10.1182/blood.V99.10.3735.