

Original Article

Running Title: Cytogenetics in Plasma Cell Myeloma

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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. Therefore, 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

Introduction

A plasma cell neoplasm is characterized by the accumulation of monoclonal plasma cells in the bone marrow. This malignancy is a clinicopathologic 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 workup 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 to 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 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 specified via immunohistochemistry and the flow cytometry was determined by use of the following markers: CD38, CD138, kappa, lambda, CD56, and CD19.

For cytogenetic evaluation, a 72-hour unsynchronized culture was performed with the following steps: adding 1ml 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

Forty-two 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 male, 14(35%) were female, and the gender ratio was 1.85:1(M:F). Subjects' median age was 62 ± 12.6 years. Median plasma cell percentage was $39 \pm 21.2\%$. 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. 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 (Figure 2-3). 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 heterogeneity, 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

Among chromosomal structural abnormalities, chromosome 1 aberrations were the most common. Whole arm unbalanced translocation of 1q known as jumping 1q translocation were 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 confounding 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 lymphoplasmacytoid 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.

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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 monotyctic	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)t(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),del(1)(p13),+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,XX,+X,+X,+1,+1,+3,+3,+5,+7,+7,+8,+9,+9,+10,+10,+10,+11,+11,+11,+11,+11,+12,+12,+12,+16,+16,+16,+16,+17,+17,+17,+19,+20,+20,+20,+20,+21,+21,+22,+22[3]/46,XX[12]					
Case12	84~86,XY,+1,+1,del(1)(p13),i(1)(q10),+2,+2,+2,+3,+3,+4,+4,+6,+6,+8,+9,+10,+11,+11,+11,+11,+12,+12,+13,+14,+15,+15,+15,+16,+17,+17,+17,+18,+18,+18,+19,+20,+21,+22,+22[4]/46,XY[11]					
Case 13	102,XY,+X,+X,+X,+Y,+1,+1,+1,+2,+2,+2,+3,+3,+3,+3,+3,+4,+4,+4,-5,-5,+6,+6,+6,+6,+7,+10,+11,+11,+12,+12,+12,+12,+12,+12,+12,+12,+13,+14,+14,+15,+15,+15,+16,+16,+18,+18,+18,+18,+19,+19,+20,+20,+21,+21,+21,+21,+21,+22,+22,+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

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.

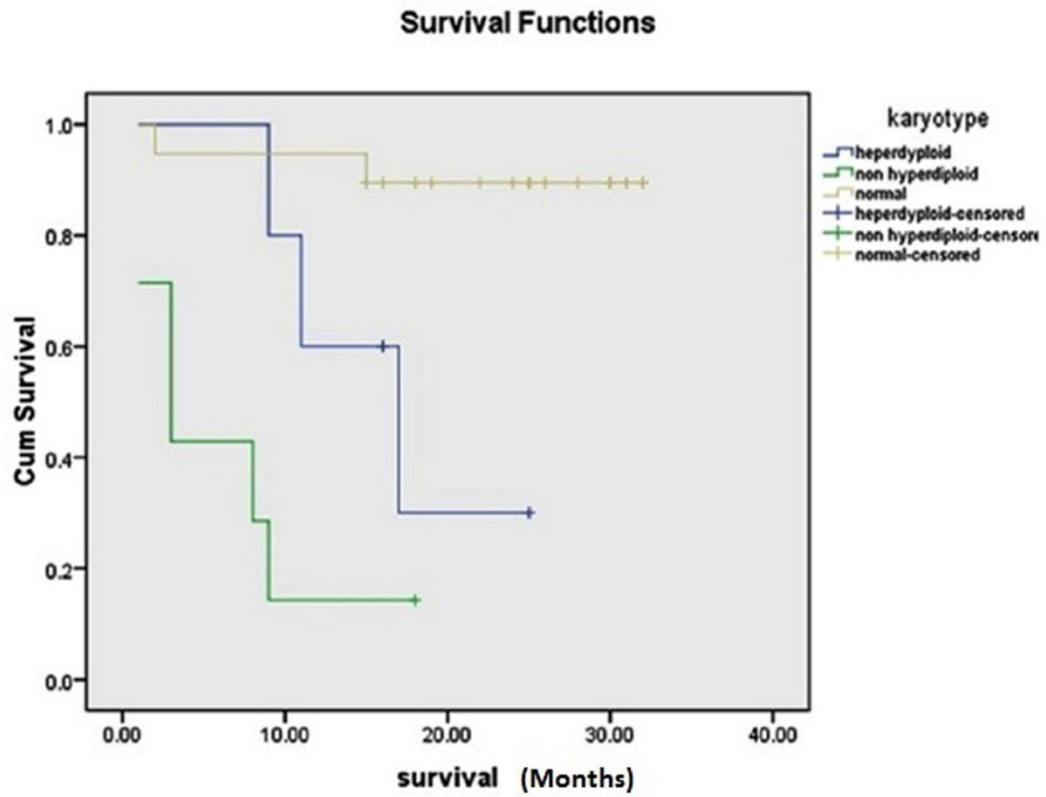


Figure 1. Kaplan Meier analysis showed a shorter survival in cases with abnormal karyotype. However, hyperdiploid cases had a better survival in comparison with non-hyperdiploid cases.

cum survival= cumulative survival

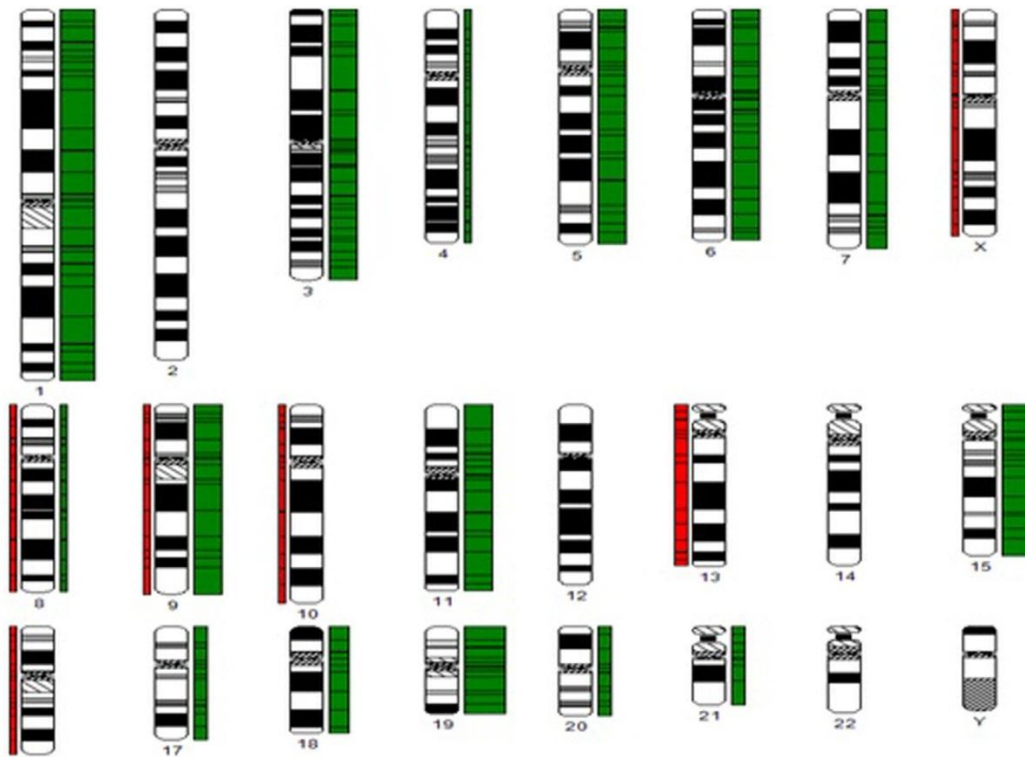
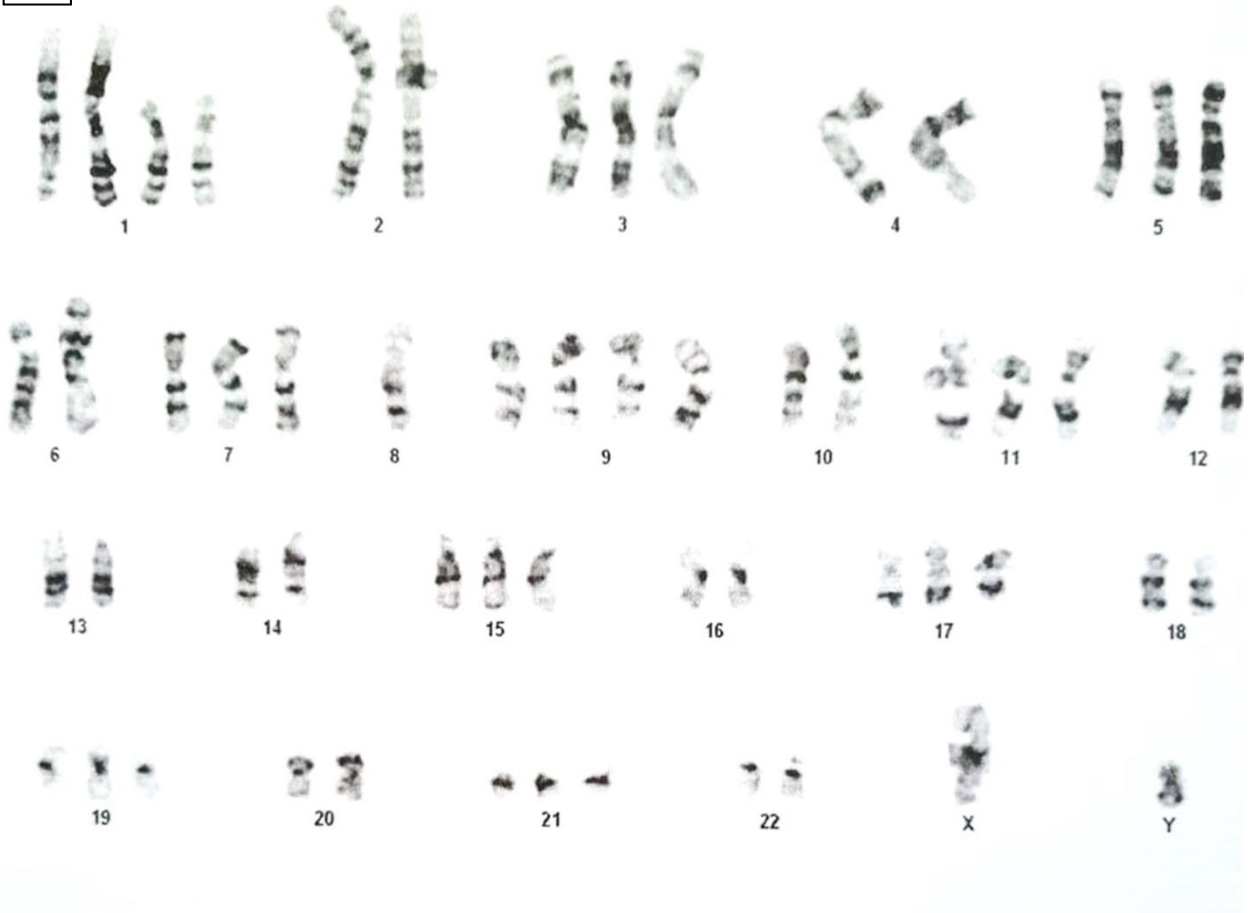


Figure 2. Cydas online software analysis of hyperdiploid cases revealed that the gain of chromosome 19 and loss of chromosome 13 were the most common numerical gain and loss, respectively (chromosome gains are shown as green bars on the right and chromosome losses are shown as red bars on the left).

A



B



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),del(1)(p13),+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).

del= deletion, ISCN= International System for Human Cytogenetic Nomenclature, der= derivative