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Monoclonal Gammopathies

Correlation between cytogenetic abnormalities and disease characteristics in multiple myeloma: monosomy of chromosome 13 and structural abnormalities of 11q are associated with a high percentage of S-phase plasma cells

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ABSTRACT

***Background and Objectives*. Cytogenetic studies in multiple myeloma (MM) are limited by the difficulties in obtaining metaphases that can be investigated and few studies have analyzed the relationship between cytogenetics and clinical disease characteristics. The aim of our study was to analyze the recurrent cytogenetic changes in MM and to correlate them with clinical and biological characteristics including the percentage of S-phase plasma cells (PCs).**

***Design and Methods.* Chromosomal abnormalities were analyzed in 86 patients with MM. In all patients, two types of cultures (5 d culture with interleukin-4 and unstimulated 72 h culture) were used for cytogenetic analysis. DNA content analysis (ploidy and cell cycle analysis) together with the most relevant clinical and biological disease features were studied.**

***Results.* Cytogenetic analysis was successful in 72 of the 86 patients (84%). Forty-seven patients (65%) had an abnormal karyotype. The most frequent trisomies involved chromosomes 3, 5, 9, 11, 15, 19, 22, 1, 7, 17, 18, and 21, and monosomies affected chromosomes 13 and 8, while structural changes involved chromosomes 1, 11, 14q32, 4p16 and 16q22-23. Patients with abnormal karyotype displayed a poor performance status, advanced stage, anemia and a high percentage of bone marrow plasma cells. In addition, MM patients with -13/13q- and 11q abnormalities showed a significantly higher proportion of S-phase PCs (p=0.02).**

***Interpretation and Conclusions.* In summary, our study shows a relationship between unfavorable cytogenetics (-13/13q-/11q abnormalities) and a high percentage of S-phase PCs, a well-known adverse prognostic factor.**
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Key words: cytogenetics, myeloma, S-phase, clinical correlation.

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Multiple myeloma (MM) is considered a clonal disorder of B-cells at the last stage of differentiation (plasma cells). Cytogenetic studies in MM are hampered by the difficulties in obtaining metaphases that can be used for analysis.[1,2] In large series of patients, abnormal karyotypes have been reported in less than 50% of MM cases.[3-8] Different cytokines can be added to the culture medium to improve the detection of chromosomal abnormalities[9-11] and a previous study[12] reports chromosomal abnormalities in 64% of MM cases using interleukin (IL-4)-stimulated cultures. Moreover little information concerning the correlation between cytogenetics and clinical features in newly diagnosed MM has been published.[5,7,13] Here, we present the cytogenetic findings from a cohort of MM patients (n=86). In addition, we have correlated the cytogenetic findings with the most relevant clinical and biological features of the disease, including DNA ploidy and cell cycle analysis in 67 patients studied at diagnosis.

Design and Methods

Patients

Eighty-six patients with MM diagnosed according to the criteria of the *Chronic-Leukemia-Myeloma Task Force*[14] were included in the study: 67 (78%) were analyzed at diagnosis, 11 (13%) at relapse or progression and 8 (9%) were studied in plateau phase after treatment. The patients' median age was 69 years (range 45-90); there were 46 male and 40 female patients. Bone marrow plasma cell infiltration ranged from 8-100% with a median infiltration of 40%. According to Durie and Salmon's clinical staging system,[15] 16% of the patients were in stage I, 35% in stage II and 49% in stage III. The monoclonal component was IgG in 49% of the cases, IgA in 33%, Bence-Jones in 14% and IgD in the remaining 3% of patients. In one case no mono-

clonal serum protein was found. The following variables were studied at diagnosis in each patient in order to analyze the relationship between clinico-biological parameters and the karyotype: age, sex, albumin, β_2-microglobulin, bone marrow plasma cells, calcium, clinical stage, creatinine, ECOG score, hemoglobin, LDH, DNA content by flow cytometry and number of PCs in S-phase.

Cytogenetic analysis

Bone marrow cells were cultured in RPMI medium supplemented with 15% fetal calf serum, penicillin and L-glutamine. In all patients, two types of culture were set up: a) 5 d culture with IL-4 (kindly provided by Schering-Plough, New Jersey, USA, 500 IU/mL medium) and b) unstimulated 72 h culture. Both types of culture were processed according to the methodology previously described.[12] Chromosomes were identified by G-banding and karyotypes were described according to the ISCN, 1995.[16] We considered a clone to be abnormal when the same structural rearrangement or chromosome gain was present in at least two mitoses or when chromosome loss was found in at least three metaphases. A karyotype was considered to be normal when no clonal chromosomal abnormalities were detected among 20 metaphases examined. Karyotypes with more than three chromosomal abnormalities and at least one structural anomaly were considered complex karyotypes.

DNA measurements assessed by flow cytometry

DNA content analysis (ploidy and cell cycle analysis) was performed according to previously described methods.[17,18] The DNA index was calculated as the ratio of the modal channel obtained for plasma cells ($CD38^{+++}$) and the remaining normal cells ($CD38^-$ or $CD38^+$) present in the sample. In addition, the proportion of cells in the different cell-cycle phases for both subsets (plasma cells and residual normal cells) was calculated according to previously described criteria[18,19] using the MODFIT software (Verity Software House, Topsham, ME, USA) after excluding cell doublets and separately gating plasma cells and residual normal cells.

Statistical methods

Student's t-test was used to estimate the significance of the differences observed between means. The chi-squared test with Yate's correction was used for comparison of dichotomic variables. Data were analyzed using the SPSS statistical program (SPSS/PC, SPSS Inc., Chicago, IL, USA).

Results

Cytogenetic analysis was successful in 72 of the 86 patients (84%). Forty-seven patients (55% of the total and 65% of the cases with assessable metaphases) had an abnormal karyotype. All but two karyotypes showed a mixture of normal and abnormal cells. Although the proportion of abnormal karyotypes detected at relapse or progression of the disease (64%) was slightly higher than that observed at diagnosis (55%), this difference was not statistically significant (p=0.23). The median number of abnormal chromosomes per case was 4 (range 1-18). Of the 47 patients with abnormal karyotypes, 20 (43%) displayed hyperdiploidy (8 had more than 50 chromosomes and 12 had between 47 and 50); 19 (40%) showed hypodiploidy (3 had nulisomy Y as a single abnormality); and the remaining 8 (17%) pseudodiploidy. Using DNA cell content analysis by flow cytometry, 65% of cases showed a DNA index > 1 (hyperdiploidy); in 31% the DNA index was 1 and in only 4% was it less than 1 (hypodiploidy). A positive correlation between DNA content and modal chromosome number was observed in patients with hyperdiploid karyotypes (r=0.83). In contrast, there was no correlation in the remaining cases; only two of the 19 patients with a hypodiploid karyotype had a DNA index < 1.

In 25 cases a combination of numerical and structural abnormalities was observed. Sixteen patients displayed structural changes alone, while numerical changes were the only chromosomal abnormality in six cases. A complex karyotype was detected in 19 patients (40%). Complete karyotypes are listed in Table 1. Karyotypes of cases #1-7, 14, 15, 19, 21, 22, 24, 25, 27 and 28 have been published previously.[12]

Numerical abnormalities

The most frequent trisomies involved chromosomes 3 (19% of the patients with abnormal karyotypes), 5 (17%), 9 (17%), 11 (17%), 15 (17%), 19 (17%), 22 (13%), 1 (11%), 7 (11%), 17 (11%), 18 (11%), and 21 (9%) (Figure 1A). In 13 cases, a combination of several of these trisomies was present with a median of 5 trisomies per case. Except in 2 cases, all the trisomies previously enumerated were present in hyperdiploid karyotypes. Monosomies affected chromosomes 13 (21% of the patients with abnormal karyotypes), 8 (19%), 20 (11%), 22 (11%) and X (11%) (Figure 1A). Monosomy 13 was associated with other chromosomal abnormalities in all cases.

Structural abnormalities

Structural changes of chromosome 1 were the most frequently observed (Figure 1B). Thus, 22

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Table 1. Abnormal karyotype in 47 patients with MM.

Case/Reference	*Karyotype*	*S-phase*
1/266	45,XY,+dic(1;11)(p36;p15),+add(7)(q36),+del(7)(q21q31),dic(9;10)(p24;p15), add(11)(p15),-13,-15,add(16)(q23),-18,add(19)(q13),-20,-21,-22,+mar1, +mar2,+mar3[10]/46,XY[6]	3.0
2/402	45,XX,+del(1)(p31),+2,der(4)t(1;4)(p32;p16),-12,-13,add(14)(q32), add(17)(q25),-18[cp11]/46,XX[12]	2.2
3/369	46,XY,-9,del(12)(p11p13),-13,der(14)t(1;14)(q22;q32),+der(14)t(1;14)(q22;q32), -18,del(20)(q11q13),+mar1,+mar2[cp20]/46,XY[5]	6.2
4/469	45,XX,-22[5]/46,XX,[10]	3.1
5/504	45,XX,-13[4]/45,idem,i(1)(q10)[3]/46,XX[17]	9.5
6/516*	44,XX,+1,-8,-20,-22[3]/46,XX[20]	1.3
7/76	43-45,X,-X,del(1)(p31),del(6)(q16q22),der(7)t(7;18)(p22;q11), +der(7)t(7;13)(p22;q11),-8,-13,add(17)(q24)[cp8]/46,XX[6]	5.0
11/585°	55,XY,+1,+del(1)(p21p36),+der(2)t(2;11)(p23;q13),+3,+9,+11,-13,+15, +add(17)(q25),+19,+20[4]/46,XY[8]	6.6
14/685	46,XX,t(11;14)(q13;q32)[5]/47,XX,+19[3]/46,XX[7]	3.9
15/20*	46,XX,t(1;16)(q21;q22)[2]/46,XX[17]	5.5
19/1240	53,XY,+dic(1;3)(p12;q27),+3,+7,-8,+9,+add(11)(q23),-13,-13,+15,+18,+19,+22, +mar[18]/46,XY[15]	2.8
21/1272	53,XY,+3,+5,+9,+11,+14,+15,+16[5]/46,XY[10]	0
22/858	47,XX,dic(1;11)(p11;q11),add(4)(p16),del(5)(q13q31),-8,+i(9)(q10),-16, der(17)t(11;17)(q13;p11),+19,+20,+22[28]/46,XX[1]	14.4
24/874	47,XX,del(6)(q16q22),+mar[13]/46,XX[9]	3.8
25/632°	53,XX,+1,+3,+5,+9,+15,+17,+18[5]/46,XX[20]	5.0
27/992	56,XY,+3,+5,+7,+9,+9,+11,+14,+15,-16,+19,+21,+22/57,idem,add(17)(q25), +18[15]/46,XY[5]	0.6
28/1136*	61,X,-X,del(1)(q31),+del(1)(p31),+2,+3,+5,+6,+7,+9,+11,+15,+16,+17,+18,+19, +20,+21,+22[12]/46,XX[10]	1.3
31/19°	41-44,X,-X,+del(1)(p21),-4,-6,-8,t(11;14)(q13;q32),-13,+mar1,+mar2[cp6] /46,XX[4]	8.2
32/47°	47,XY,+10[3]/46,XY[10]	ND
34/74	45,X,-X[4]/46,XX[7]	0.3
35/81	44,XY,-8,-13[3]/46,XY[10]	0.3
36/82	45,X,-Y[5]/46,XY[9]	2.6
40/115	45,XY,-19[5]/46,XY[3]	2.3
41/132	44,XX,-4,-6[3]/46,XX[10]	0.5
42/164	47,XX,+der(3)t(3;5)(p26;q11),-8,-10,der(11)t(3;11)(q12;p15),add(14)(q32),+17, +18[2]/46,XX[17]	1.9
43/362	48-52,XX,del(1)(q22q42),dup(4)(q25q31),+der(5)t(1;5)(q32;q34),+del(6)(q21q24), +der(6)t(1;6)(q21;q21),+7,+add(7)(p22),+11,t(11;14)(q13;q32),-14,+17[cp7] /46,XX[5]	6.5
46/750	46,XX,t(8;22)(q24;q11),der(10)t(1;10)(q12;p13),add(11)(p14), del(13)(q13q21)[10]/46,XX[7]	ND
47/954	45,XX,-8[4]/46,XX[19]	2.8
49/1019	46,XY,del(13)(q21q31)[3]/46,XY,idem,del(4)(p13p16)[2]/46,XY[3]	0
51/672	47-49,X,-Y,add(1)(p11),add(3)(p24),-4,+5,del(6)(q21q24),+7,+add(7)(q36), -13,+add(16)(q23),+19,-20,+mar1,+mar2[cp9]	35.4
52/122	44,X,-Y,-20[3]/46,XY[11]	1.1
56/600°	46,XY,del(1)(q21),der(4)t(1;4)(q21;q35)[10]	ND
60/355	47,XX,i(1)(q10),+5,der(11)t(1;11)(p31;q23),del(14)(q13q32)[5]/46,XX[4]	2.0
61/360	45,XX,-10[4]/46,XX[8]	1.6
63/485	45,X,-Y[3]/46,XY[9]	2.8
64/1371	47,XY,del(1)(q21q42),-2,+3,+5,-8,+9,-10,+11,der(15)t(1;15)(q21;q26)[7] /46,XY[15]	0.1
69/1438	47,XY,+mar[3]/46,XY[12]	3.0
70/1363	46,XX,add(1)(p31)[3]/46,XX[11]	1.3
73/758°	46,XY,+1,dic(1;19)(q10;p13),t(11;14)(q13;q32)[6]/47,idem,+15[2]/46,XY[3]	2.9
74/1719°	47,XY,+19[2]/46,XY[16]	0
75/1752	52,XY,+X,del(1)(p12),+del(1)(p12),+del(1)(q12),+3,add(8)(q24),+11,-14, +21,+22[5]/46,XY[6]	0
76/1708	43,XY,-1,der(4)t(1;4)(q31;p16),der(5)t(5;11)(q34;q13),+6,add(12)(p13),-14, der(16)t(1;16)(q31;q23),-17,-22[9]/46,XY[5]	0
77/1880	45,X,-Y[9]/46,XY[5]	0.9
80/2106	46,XY,dup(4)(q28q35)[2]/46,XY[13]	0
83/2291	39,Y,-X,del(1)(q21q42),-4,del(9)(q22q33),del(11)(q21q23),add(11)(q23),-13,-15, -19,-20,-21,-22,+mar[6]/46,XY[2]	17.8
85/2025	47,XX,add(14)(q32),+mar[2]/46,XX[8]	0.8
86/955	62,XY,+1,+1,+3,+4,+5,+8,+9,+13,+14,+15,+17,+18,+21,+22,+mar1,+mar2[2] /46,XY[7]	0

**Plateau phase after treatment. °Relapse or progression. ND: not done.*

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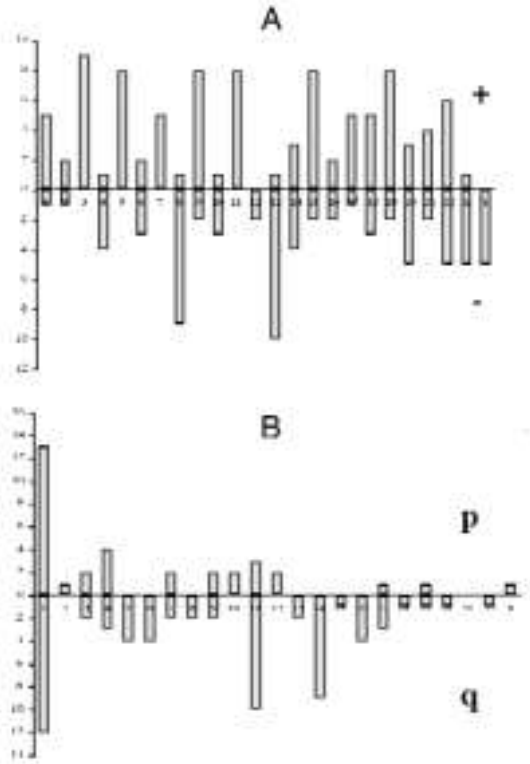

Figure 1. Frequency of numerical (A) and structural (B) chromosomal anomalies in 47 patients with MM. *+: trisomies. –: monosomies. p: short arm. q: long arm.*

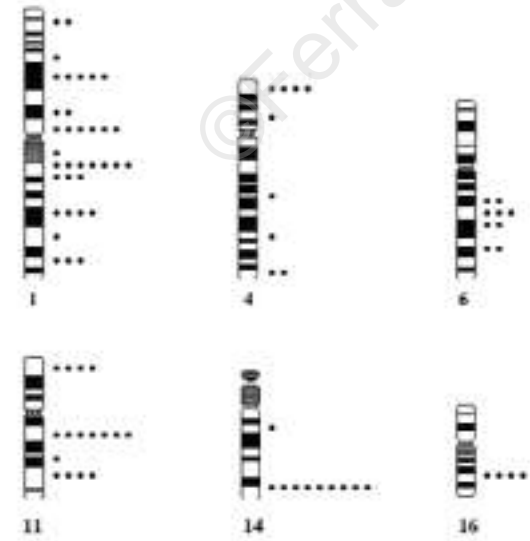

Figure 2. Schematic representation of the breakpoints involved in structural abnormalities in 47 patients with MM.

of the 47 patients (47%) with clonal abnormalities had structural abnormalities in chromosome 1:1p was involved in 9 cases, 1q in another 9 cases and structural rearrangements involving both arms of chromosome 1 were found in 4 cases. Partial trisomy for all or part of 1q was found in 13 cases. In four cases structural changes in chromosome 1 were the single cytogenetic abnormality. Breakpoints were clustered around pericentromeric regions (Figure 2). Structural abnormalities of chromosome 11 were identified in 10 patients (21%) with bands 11q13 and 11q23 involved in 7 and 3 cases, respectively. Chromosomal rearrangements of band 14q32 were found in 8 patients (17%) and 4 of these corresponded to a t(11;14)(q13;q32). Other bands recurrently involved were 4p16 (9%) and 16q22-23 (9%). Deletions of the long arm of chromosome 6 including bands q16-q24 were detected in 4 patients (9%) (Figure 2).

Clinical parameters and karyotype

Associations between chromosomal abnormalities and clinico-biological features of MM were assessed in patients studied at the time of diagnosis (n=67). Along with a correlation with the most relevant clinico-biological parameters in MM, one additional goal was to evaluate whether or not specific chromosomal abnormalities were related to the percentage of S-phase PCs. Based on the most recurrent abnormalities detected in the present study and on the prognostic results obtained by Tricot *et al.*,[8,13] six cytogenetic groups were established: 1) abnormal karyotype; 2) partial or complete deletions of chromosome 13 and structural abnormalities involving 11q (-13/13q-/11q); 3) complex karyotype; 4) structural abnormalities of chromosome 1 (1p/1q); 5) structural abnormalities of 14q; and 6) monosomy 8. MM patients with abnormal karyotype showed a poor performance status, advanced stage, low hemoglobin levels and a high percentage of bone marrow PCs as compared with those patients with normal chromosomes (Table 2). In addition to these clinical associations, patients with -13/13q-/11q and patients with a complex karyotype had high serum calcium values. Interestingly, patients with -13/13q-/11q displayed a significantly higher proportion of S-phase PCs. Upon considering all cases with any type of cytogenetic abnormality (abnormal karyotype group) the association with the percentage of PC in S-phase disappeared (Table 2). It should be noted that age, β_2-microglobulin, albumin, and LDH were not associated with any cytogenetic group. Patients with 1p/1q abnormalities but without coexisting changes on chromosomes 11 and 13 did not show distinct clinico-

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Table 2. Associations between clinico-biologic parameters and cytogenetic abnormalities in MM.

	–13/13q–/11q	*Rest*	*p*
ECOG ≥ 2	13/15 (87%)*	17/41 (42%)	0.003
Stage III	13/15 (87%)	17/42 (41%)	0.002
Hemoglobin (g/dL)	9.1 (2.5)°	10.7 (2.7)	0.04
Calcium (mg/dL)	11.7 (2.8)	10.2 (1.4)	0.02
BMPC (%)	58.8 (24.8)	41.0 (21.6)	0.01
S-phase (%)	7.4 (9.7)	1.8 (1.9)	0.02
	Abnormal karyotype	*Normal karyotype*	*p*
ECOG ≥ 2	25/36 (69%)	5/20 (25%)	0.001
Stage III	24/37 (65%)	6/20 (30%)	0.01
Hemoglobin (g/dL)	9.6 (2.6)	11.5 (2.4)	0.01
BMPC (%)	51.3 (24.9)	35.2 (17.2)	0.01

*Results expressed in *percentage or °mean (SD). BMPC: bone marrow plasma cells.*

biological profiles. No significant clinical correlation was found for the group of patients with 14q abnormalities and the group with monosomy 8.

Discussion

Cytogenetic studies are a powerful tool in the study of hematologic malignancies. Associations between cytogenetic changes and clinico-biological characteristics have been found in acute leukemias.[20,21] In MM, some studies have correlated the chromosomal abnormalities with survival, but little attention has been paid to the correlation of cytogenetic findings with clinical and biological disease characteristics of MM patients, probably because of the low incidence of clonal changes found in MM.[5,7,13] The 65% incidence of abnormal karyotypes found in this study is the highest reported so far in a large series of patients.[3-9,22] The MM studies that include series of patients at different disease status have shown a higher proportion of abnormal karyotypes in patients at relapse or progression.[3-6] In contrast, the present study showed no significant differences with respect to the incidence of abnormal karyotypes at diagnosis, relapse or progression. The use of IL-4-stimulated cultures could help to increase the proportion of detected clonal abnormal mitoses even in patients studied at diagnosis as we previously reported.[12]

In our study, the incidence of hypodiploid karyotypes was similar to that of hyperdiploid karyotypes. Upon comparing ploidy by cytogenetics and flow cytometry, a correlation was found between modal number and DNA index within cases with hyperdiploid karyotypes. By contrast, the proportion of cases with a DNA index < 1, as detected by flow cytometry, was lower than the incidence of hypodiploid cases by karyotypic analyses. This fact supports the previously described limited ability of flow cytometry to detect minor changes in cell DNA contents, such as a loss of only one chromosome.[2,23] Indeed, most of the hypodiploid karyotypes reported here are the result of a loss of only one chromosome. As described in other studies, a high proportion of abnormal cases showed complex karyotypes (40%). Trisomies of chromosomes 3, 5, 9, 11, 15 and 19 and monosomies of chromosomes 13 and 8 represented the most common numerical abnormalities, in accordance with previous reports (reviewed by Zandecki *et al.* and Feinman *et al.*) The association of trisomies with hyperdiploid karyotypes and the association of partial or complete deletion of chromosome 13 with hypodiploid and pseudodyploid karyotypes is consistent with the two different cytogenetic patterns depending on the chromosome number described by Smadja *et al*.[25] Almost half of the patients (47%) showed structural abnormalities of chromosome 1, associated in all but 4 cases with other abnormalities. Partial trisomies for the 1q segment have been widely reported in human malignancies, including B-cell lymphomas and have been considered to represent secondary karyotype evolution during the progression of the disease, rather than a primary event.[26,27] Breakpoints involving 14q32 were the most frequently detected, and t(11;14)(q13;32) the most common 14q32 translocation observed in our series. However, the incidence of structural rerrangements of 14q32 detected by conventional cytogenetics in MM[5-7,22] is quite low when compared with analyses of immunoglobulin heavy chain (IgH) gene rearrangements using Southern blot and fluorescence *in situ* hybridization (FISH) which have revealed illegitimate IgH gene rearrangements in 75% of MM.[28,29] This fact reveals the high incidence of cryptic translocations involving the IgH gene in MM. Thus, t(4;14)(p16;q32) which leads to the deregulation of FGFR3 and MMSET genes is highly recurrent by using FISH studies but undetectable using chromosome morphology.[30] In the present study abnormalities affecting 4p16 were found in 4 cases (9%), but in none of them was the 14q32 band identified as the partner chromosomal region (Table 2). Nevertheless, the incidence of 4p abnormalities in our work is the highest reported in cytogenetic studies until now.[31] We found rearrangements involving 16q22-23 in 4 cases (9%). This anomaly has been detected only rarely using a G-banding

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technique.[22] However, t(14;16)(q32;q22-23), which has been associated with C-MAF overexpression, has recently been identified as a recurring aberration in MM by using multicolor spectral karyotyping (SKY).[32] In our study the14q32 region was not involved in 16q22-23 anomalies. These findings suggest the existence of chromosome partners, other than 14q32, that are implicated in translocations with chromosomal regions, such as 4p and 16q22-23, which appear to have a relevant role in the pathogenesis of MM.[33,34] In this study we also evaluated the relationship between cytogenetic abnormalities and clinicobiological characteristics of the disease in MM patients at diagnosis. Consistent with other reports, it was found that abnormal karyotype was significantly associated with a poor performance status, advanced stage, low hemoglobin levels and a high percentage of bone marrow plasma cells.[5,7,8,35,36] In addition we found that, in patients with -13/13q-/11q abnormalities, both serum calcium values and S-phase PC percentage were higher. By contrast, age, β_2-microglobulin, albumin and LDH were not associated with any of the cytogenetic groups established in this study. It has been reported that -13/13q-/11q abnormalities confer a poor prognosis in MM[13] but in this previous study, correlation with cell cycle analyses was not reported.

Although it could be speculated that any abnormal karyotypes in MM are an expression of a hyperproliferative disease, this was not the case in our series of patients, since the association between high S-phase PCs and chromosomal changes was restricted to -13/13q-/11q abnormalities. In addition, MM cases with other cytogenetic changes did not show a correlation with a hyperproliferative state of PC. In summary, our study shows a relationship between unfavorable cytogenetics (-13/13q-/11q abnormalities) and high percentage of S-phase PCs, a well-known adverse prognostic factor.[37,38]

Contributions and Acknowledgments

NCG: design, cytogenetics and writing of the paper. JMH: statistical analysis and review. JLG: cytogenetics. JA and GM: flow cytometry studies. MBG: cytogenetics. JH and JFC: clinical data and collaboration in analysis of data. JFSM: review and final approval. We thank the hematologists of Castilla-León, Spain for providing us clinical data, and P.Fernández, M.A. Hernández and M. Anderson for excellent technical assistance.

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Disclosures

Conflict of interest: none.

Redundant publications: karyotypes of 16 cases were published previously in a paper by Hernández JM, Gutiérrez NC, Almeida J, et al.

Manuscript processing

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Potential implications for clinical practice

- Unfavourable cytogenetics (-13/13q-/11q abnormalities) are associated with a well-known adverse prognostic factor in MM.
- Cytogenetic studies are relevant in the evaluation of MM patients at diagnosis.

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