Timing of acquisition of deletion 13 in plasma cell dyscrasias is dependent on genetic context

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ABSTRACT

Background
Multiple myeloma, monoclonal gammopathy of undetermined significance and smoldering multiple myeloma harbor common chromosomal abnormalities but the prevalence and relative association of aberrations in these diagnostic groups remains controversial. We investigated these aspects in a large series of patients.

Design and Methods
Chromosome 13 deletion (Δ13), deletion of *TP53*, ploidy status and immunoglobulin heavy chain (*IgH*) translocations were evaluated by fluorescence *in situ* hybridization in patients with monoclonal gammopathy of undetermined significance (n=189), smoldering multiple myeloma (n=127) and multiple myeloma (n=400).

Results
Overall, Δ13 (25%, 34% and 47%), 16q23 deletions (6%, 8% and 21%) and 17p13 deletions (3%, 1% and 10%) were less frequent in patients with monoclonal gammopathy of undetermined significance and smoldering multiple myeloma than in those with multiple myeloma. When distinct genetic groups were considered, no differences in the prevalence of Δ13 were found with t(4;14)(p16;q32) and t(14;16)(q32;q23) among the three diagnostic groups; in contrast Δ13 was rarer in t(11;14)(q13;q32) in patients with monoclonal gammopathy (1/28) and smoldering myeloma (2/13) than in those with multiple myeloma (40%). Similar results were seen for the few t(6;14)(p21;q32) cases: 0/3 patients with monoclonal gammopathy or smoldering myeloma had the Δ13, whereas 4/6 (67%) patients with multiple myeloma and this translocation also had the deletion. In multiple myeloma patients with both an *IgH* translocation and Δ13, the proportions of cells affected by the two abnormalities were similar, as was the case for t(4;14) and t(14;16) monoclonal gammopathy patients positive for Δ13. In contrast, in monoclonal gammopathy patients with t(14;20)(q32;q11), the translocation was present in almost all cells, while the Δ13 was present in only a sub-population.

Conclusions
These results indicate that the presence and time of occurrence of Δ13 depends on the presence of specific concurrent abnormalities. The observation that Δ13 was extremely rare in monoclonal gammopathy of undetermined significance and smoldering multiple myeloma with translocations directly involving *cyclin D* genes (*CCND1* and *CCND3*) suggest a possible role of Δ13 in the progression of the disease specifically in these genetic sub-groups. *(clinicaltrials.gov identifier: ISRCTN 68454111; UKCRN ID 1176).*

Key words: deletion 13, plasma cell dyscrasias, genetic context.

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Introduction

Monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM) are characterized by an expansion of monoclonal plasma cells and both can progress to symptomatic multiple myeloma (MM) or other related conditions.[1-3] MGUS is the most frequent plasma cell disorder and its incidence increases markedly with age, reaching approximately 3% in subjects over 70 years old.[1,3-5] MGUS is defined by a serum M-protein concentration of less than 30 g/L and fewer than 10% of plasma cells in the bone marrow, while patients with SMM meet the diagnostic criteria for MM but are asymptomatic. SMM resembles MGUS in that end-organ damage is absent, but clinically it is far more likely to progress to active MM or amyloidosis.[3]

The paucity of plasma cells within the bone marrow of patients with MGUS, together with the low proliferative capacity of these cells, has precluded significant karyotypic studies in these patients. Interphase fluorescence *in situ* hybridization (FISH) provides an alternative approach to investigate chromosomal aberrations in tumor cells from which metaphases are difficult to obtain. Using interphase FISH, chromosomal aberrations were consistently detected in a high proportion of MGUS patients, with roughly 50% of them carrying one of the primary *IgH* translocations and the remaining patients displaying a hyperdiploid karyotype. These findings suggested that ploidy status and *IgH* rearrangements were early events delineating different pathogenic pathways.[6-9]

Conflicting results have been reported on the prevalence of deletion/monosomy 13 (Δ13) in MGUS. Avet-Loiseau *et al*. found a substantially lower frequency of this abnormality in MGUS (~25%) than in MM (~50%),[10,11] while others reported a similar incidence in both conditions.[7,12] Fonseca *et al*. also indicated that when Δ13 was detected in MGUS it occurred in the majority of clonal plasma cells,[7] consistent with that normally observed in MM,[13,14] while others reported a greater heterogeneity in MGUS.[13] There has also been controversy regarding the prognostic significance of Δ13 in MM. This chromosomal aberration, detected by interphase FISH, was one of the first established genetic prognostic factors, independent of the mode of treatment.[15] However, it now appears that the dismal prognosis previously thought to be conferred by the deletion is actually due to its association with other poor-risk genetic markers, such as specific primary *IgH* translocations or *TP53* deletions,[16,17] and that Δ13 on its own probably does not affect prognosis.

In this study, we used interphase FISH to assess the incidence and the association of Δ13 with *IgH* translocations, ploidy status and deletions of 16q23 and *TP53* in a large series of MGUS and SMM patients. We compared the results with the frequencies found in a group of newly diagnosed MM patients in order to determine whether the patterns of chromosomal aberrations differ within the different diagnostic groups. We also explored the clonal heterogeneity of MGUS by comparing the frequencies of the different chromosomal aberrations detected in individual patients.[10]

Design and Methods

Patients

We evaluated a consecutive series of 716 patients with plasma cell disorders reported to the LRF UK Myeloma Forum Cytogenetic Database between November 2000 and January 2007. Samples were received from different centers throughout the UK with informed consent for cytogenetic/FISH analysis. The cohort consisted of 189 patients with MGUS (median age, 69 years; range, 36-92 years) and 127 with SMM (median age, 69 years; range, 31-89 years) not requiring therapy, and 400 newly diagnosed MM patients entered into the MRC Myeloma IX Trial (median age, 64 years; range, 30-89 years). Patients with an IgM heavy chain subtype were not eligible for this study, given the different biology of this disease.[15] Patients were classified as having MGUS or SMM according to standard criteria[18] and were required to have no evidence of organ damage indicative of MM. All but four SMM and eight MGUS patients were studied at diagnosis.

Cytogenetic testing

Density gradient centrifugation of bone marrow aspirates over Lymphoprep was performed to separate mononuclear cells by standard protocols. $CD138^+$ plasma cells were isolated by magnetic-activated cell sorting using anti-CD138 immunobeads (Miltenyi Biotec Ltd., Bisley, UK). Interphase FISH was performed on plasma cells using a panel of commercial and in-house probes, as previously described.[19,20] Results were available for Δ13, *IgH* rearrangements, t(4;14)(p16;q32), *CCND3* break-apart (6p21), t(11;14)(q13;q32), t(14;16)(q32;q23), *MAFB* break-apart (20q11), deletion of *TP53* (17p13) together with 17 centromere, and ploidy status. The interphase FISH method used to estimate ploidy and classify patients into groups with and without hyperdiploidy had been previously designed and assessed in MM patients,[20] using a modification of the method described by Wuilleme *et al.*[21] Break-apart patterns for the *CCND3* or the *MAFB* probes in cases with a concomitant break-apart of the *IgH* probe were suggestive of t(6;14) and t(14;20), respectively. Cases with a suspected t(14;20) were tested using a fusion probe approach to confirm the presence of the translocation.

The cut-off levels for interphase FISH scoring recommended by the European Myeloma Network (EMN) FISH workshop (10% for fusion/break-apart probes and 20% for numerical abnormalities) were followed.

Statistical analysis

The frequencies of chromosomal aberrations in the groups of patients were compared by Fisher's exact test or the Kruskall-Wallis test, as appropriate.

Results

Frequencies of chromosomal abnormalities

FISH analysis was performed according to the availability of patients' material: a minimum of seven loci were tested (4p16, 5p15, CEP 9, 11q13, 13q14, 14q32 and CEP 15). In more than 80% of patients, 12 different loci were

analyzed. We observed copy number changes or structural alterations for at least one of the chromosomal regions tested in 169/189 (89%) MGUS, 124/127 (98%) SMM and 396/400 (99%) MM.

Table 1 summarizes the frequencies of the specific chromosomal aberrations within each diagnostic group. The incidence of Δ13 was substantially lower in MGUS (25%) and SMM (34%) than in MM (47%); the difference across the three groups was statistically highly significant (Kruskall-Wallis test: MGUS *versus* SMM *versus* MM, $p<0.001$).

Rearrangements involving the *IgH* heavy chain locus located at 14q32 were detected with similar frequencies in MGUS and MM (41% and 46%, respectively); the incidence in SMM (35%) was lower, but the difference was not statistically significant. When the individual chromosomal partners of the primary translocations were considered, similar frequencies of t(6;14), t(11;14) and t(14;16) were observed among the three groups; t(4;14) was rare in MGUS (4%), but was observed at the same incidence in SMM and MM (13%) (MGUS *versus* MM, $p<0.001$). The frequency of t(14;20) was higher in MGUS (5%) than in either SMM (0%) or MM (2%). The difference in the incidence of this translocation was not statistically significant in this analysis, but became so when the incidence in the same MGUS group was compared to that in a larger population of MM patients (*unpublished data*). Deletion of 16q23 was found to be less common in MGUS (6%) and SMM (8%) than in MM (21%) (MGUS *versus* MM, $p<0.001$). Deletion of *TP53* was also very rare in MGUS (3%) and SMM (~1%).

Patients with MGUS and SMM were classified as being hyperdiploid or not in the same way as previously described for MM.[20] The distribution into the two ploidy classes differed between the diagnostic groups. A hyperdiploid karyotype was indicated in 63% of SMM and 57% of MM patients, while only 42% of MGUS cases were assigned to this category. The non-hyperdiploid MGUS group also included those patients found to be negative for all the interphase FISH tests performed; in MGUS these patients represented 11% of the total group and accounted for most of the difference between the groups.

IgH rearrangements involving the five recurrent loci (4p16, 6p21, 11q13, 16q23 and 20q11) were highly associated with a non-hyperdiploid karyotype in all three diagnostic groups: 94% of MGUS cases, 82% of SMM cases and 73% of MM cases with one of these *IgH* translocations were found in the context of non-hyperdiploidy ($p<0.001$ for all diagnostic groups). In contrast 35 of 49 MM cases with an *IgH* rearrangement not involving one of these loci were found in association with hyperdiploidy ($p=0.043$). In the SMM group the six unidentified *IgH* rearrangements were equally distributed between the two ploidy groups. In MGUS, 12 of 16 unidentified *IgH* rearrangements were found in the context of a non-hyperdiploid karyotype but the association was not statistically significant ($p=0.18$).

Table 1. Incidence of specific chromosomal abnormalities in the three groups of patients with MGUS, SMM and MM.

Chromosomal abnormalities	MGUS n=189 Number of pts (%)	SMM n=127 Number of pts (%)	MM n=400 Number of pts (%)	*p* value MGUS *vs.* SMM	*p* value MGUS *vs.* MM	*p* value SMM *vs.* MM
Δ13[†]	47/185 (25%)	42/123 (34%)	186/395 (47%)	0.12	<0.001	0.012
IgH rearrangement	78/189 (41%)	44/125 (35%)	183/398 (46%)	0.29	0.28	0.038
t(4;14)	7/184 (4%)	16/122 (13%)	50/400 (13%)	0.003	<0.001	0.87
t(6;14)	2/176 (1%)	1[††]/118 (~1%)	6/393 (2%)	1	1	1
t(11;14)	29/186 (16%)	13/122 (11%)	55/399 (14%)[§]	0.23	0.61	0.44
t(14;16)	6/180 (3%)	4/119 (3%)	15/396 (4%)	1	1	1
16q23 deletion	8/140 (6%)	7/83 (8%)	75/365 (21%)	0.42	<0.001	0.011
t(14;20)	9/178 (5%)	0/118 (0%)	9/394 (2%)	0.012	0.117#	0.13
TP53 deletion	5/177 (3%)	1/116 (~1%)	38/388 (10%)	0.41	0.003	<0.001
Hyperdiploid	72/173 (42%)	70/112 (63%)	223/388 (57%)	<0.001	<0.001	0.27
Non-hyperdiploid	101/173 (58%)*	40/112 (37%)**	165/388 (43%)			

*[†]Near-tetraploid cases with only two copies of 13q14 were counted as Δ13. [††]The locus 6p21 was involved in a t(6;22)(p21;q11) with the IgL locus. *19/173 patients (11%) belonging to the non-hyperdiploid group were found negative for all the FISH tests performed and were classified as diploid (non-hyperdiploid). **2/112 patients (~2%) were negative for all the FISH tests performed. [§]2/55 (4%) patients showed amplification of* CCND1, *in the absence of t(11;14); given that both abnormalities result in over-expression of* CCND1, *they were analyzed as a single group. #When the frequency of t(14;20) in MGUS was compared to that found in a larger group of MM patients (~ 1800), the difference was highly significant.*

Percentage of plasma cells in patients with chromosome 13 deletion

When present, Δ13 involved a variable proportion of plasma cells (Figure 1). The median percentage of plasma cells carrying the abnormality was 65% in MGUS, 88.5% in SMM and 95% in MM. No variation was seen for illegitimate *IgH* rearrangements: in patients with MGUS the median percentage of cells displaying a 14q32 translocation was 91.5% (range, 24%-100%). The level of plasma cell involvement by different chromosomal aberrations was

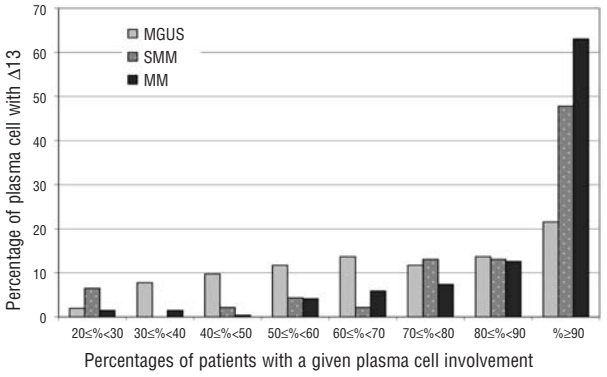

Figure 1. Distribution of the percentages of abnormal plasma cells with Δ13 in patients found positive for the abnormality, among the three groups of patients.

compared for all MGUS patients who exhibited Δ13 with at least one other abnormality (Table 2). Because of the differences in false positive rates between probes, unequivocal evidence of heterogeneity within the neoplastic clone was only accepted when the difference in the proportions of cells affected by distinct chromosomal aberrations was 30% or more. In 16 of 47 patients with Δ13, the abnormality was present in 60% or less of plasma cells (cases 1-16 in Table 2); of these 16 cases, 12 had other chromosomal aberrations for comparison. In all but three of these 12, the plasma cell involvement by the non-Δ13 abnormality was at least 30% greater than that shown by Δ13.

Interestingly five of six (83%) MGUS cases positive for both t(4;14) and Δ13 showed the same proportion (±5%) of plasma cells with the two abnormalities. In contrast, four of five (80%) cases of t(14;20) MGUS with Δ13 showed at least 30% fewer Δ13-positive plasma cells (median 51%) than t(14;20)-positive ones (median 95%). In MM, seven of nine (78%) cases of t(14;20) were associated with Δ13 and the median difference in plasma cell involvement by Δ13 and the translocation was 10% (range, 0-27%). In MGUS, 16q23 deletions were often present in a sub-clone of plasma cells (median, 63%; range, 23-100%), while in MM the median percentage of plasma cells with the abnormality was 87% (range, 21-100%). Those MGUS cases in which the proportion of plasma cells carrying the 16q deletion was small displayed at least one of the other chromosomal aberrations in the majority

Table 3. Association between Δ13 and the different chromosomal abnormalities.

	Δ13			*p* value
	MGUS	SMM	MM	
IgH rearrangement	26/76 (34%)	22/43 (51%)	110/182 (60%)	MGUS *vs.* MM $p<0.001$
t(4;14)	6/7 (86%)	13/16 (81%)	45/48 (94%)	
t(6;14)	0/2	0/1	4/6 (67%)	
t(11;14)	1/28 (3.6%)	2/13 (15%)	21/53 (40%)	MGUS *vs.* MM $p<0.001$
t(14;16)	4/6 (67%)	3/4 (75%)	11/15 (73%)	
t(14;20)	5/9 (56%)	0	7/9 (78%)	
Hyperdiploid	11/71 (15%)	14/68 (21%)	74/219 (34%)	MGUS *vs.* MM $p=0.003$
Non-hyperdiploid	32/101 (32%)	22/42 (52%)	109/164 (66%)	MGUS *vs.* MM $p<0.001$ MGUS *vs.* SMM $p=0.02$

Table 2. List of 47 MGUS patients with Δ13 ordered on the basis of the percentage of plasma cell involvement by the abnormality. For each case, concomitant numerical or structural abnormalities are specified with the percentage of plasma cell involvement (UIP, unidentified partner).

Case	% of plasma cells with Δ13	Other abnormalities (%)	Case	% of plasma cells with Δ13	Other abnormalities (%)
1	25%	Trisomy 9 (35%)	25	74%	t(4;14) (100%)
2	30%	t(14;20) (100%)	26	75%	Trisomies 5, 9 and 15 (99%), *c-MYC* split (47%)
3	36%		27	76%	t(14;16) (96%)
4	38%	Trisomy 9 (85%)	28	79%	Trisomy 5 (79%)
5	40%		29	80%	Unbalanced *IgH* split (80%) (UIP)
6	41%		30	81%	Unbalanced *IgH* split (100%) (UIP); deletion 16q23 (97%); deletion *TP53* (50%)
7	45%		31	82%	
8	45%	t(14;20) (90%)	32	81%	Trisomies 5, 11 and 15 (98%)
9	48%	t(11;14) (100%)	33	83%	Deletion 14q32 (79%)
10	53%	Trisomies 5, 6, 9 and 15 (>90%)	34	84%	t(4;14) (85%)
11	53%	Trisomies 5, 7, 15 (>90%)	35	88%	3 x "*CCND3*" (75%); trisomy and tetrasomy 9 (100%); trisomy 15 (75%)
12	56%	t(14;20) (100%)	36	90%	Deletion 14q32 (79%)
13	56%	Deletion 16q (23%)	37	90%	Trisomies 5, 9 (99%); tetrasomy 15 (88%); 3 x "*CCND1*" (76%); 3 x "*IgH*" (94%)
14	58%	Deletion 14q (67%)	38	90%	Trisomies 5, 9 and 15 (96%)
15	58%	Trisomy 9 (89%)	39	94%	t(4;14) (89%)
16	60%	t(14;20) (90%)	40	96%	Trisomies 5 & 15 (95%)
17	61%	t(14;20) (75%)	41	97%	Deletion 14q32 (93%); deletion 16q23 (33%)
18	62%	t(14;16) (60%)	42	97%	t(4;14) (94%)
19	62%	Trisomies 9 (52%) and 15 (60%)	43	100%	
20	63%	Trisomies and tetrasomies 5, 7, 9 and 15 (79%)	44	100%	Trisomy 5 (94%); tetrasomy 9 and 15 (96%); 3 x "*CCND1*" (60%)
21	65%	t(4;14) (70%)	45	100%	Deletion 14q32 (88%)
22	65%	t(4;14) (70%)	46	100%	Unidentified *IgH* split (100%) (UIP)
23	72%	t(14;16) (95%)	47	100%	t(14;16) (100%)
24	72%	Unbalanced *IgH* split (96%) (UIP)			

of clonal plasma cells (deletion 16q23 *versus* other chromosomal aberrations: 23% *versus* 82% *IgH* split; 33% *versus* 93% deletion 14q32; 44% *versus* 92% *IgH* split; 47% *versus* 99% IgH split).

Association of chromosome 13 deletion with other abnormalities

Table 3 shows the association between Δ13 and other chromosomal aberrations. The Δ13 was less frequently associated with any of the *IgH* rearrangements in MGUS than in MM (MGUS *versus* MM, 34% *versus* 60%; $p<0.001$). However, when the individual translocations were examined, no differences were found in the frequencies of association of t(4;14), t(14;16), or t(14;20) with Δ13 among the three diagnostic groups.

In MM, Δ13 was found in 40% of t(11;14) cases and involved a large proportion of plasma cells (>85%) while only one of 28 (3.6%) MGUS cases with t(11;14) had Δ13 ($p<0.001$). Furthermore, in this case, only 45% of the plasma cells had Δ13, while the translocation was present in all cells. In SMM only two of t(11;14) cases had Δ13 (15%), but this was not significantly different from the percentage found in MM. Both SMM patients had Δ13 in 70% of their plasma cells and the translocation in 100%. In this study, the presence of t(6;14) was detected in only 1-2% of patients, in agreement with other reported series. Despite the small number of cases, it was notable that Δ13 was present in four of the six (67%) MM cases, while in MGUS the two t(6;14) were both negative for Δ13 (in one of these two cases, 12% of the plasma cells carried the deletion).

Discussion

Our analysis of chromosomal aberrations in MGUS and SMM revealed a significantly lower frequency of Δ13 in the pre-malignant conditions than in MM. This is in accordance with findings reported by Avet-Loiseau *et al.*[10] The frequency of Δ13 progressively increased from MGUS to SMM to MM, suggesting a possible role of this abnormality in disease progression. The incidence of deletion of 16q23 and *TP53* also increased progressively from MGUS to MM ($p<0.001$ and $p=0.003$, respectively). In contrast, a similar frequency of *IgH* rearrangements was observed in the three groups. When the individual incidences of the specific translocations were compared, only t(4;14) was significantly less frequent in MGUS, in agreement with other reports.[7,10]

Interphase FISH was used to classify patients according to their ploidy status into those with hyperdiploidy and those without. Δ13 was found more frequently in patients with a non-hyperdiploid karyotype than in those with hyperdiploidy in all three groups of patients (MGUS, 15% *versus* 32%; SMM, 21% *versus* 52%; MM, 34% *versus* 66%), suggesting that the specific association between Δ13 and non-hyperdiploidy, extensively reported in MM,[15,17] is already established at the stage of MGUS. These findings differ from those reported by Brousseau *et al.*[22] In MGUS, they found Δ13 more frequently in patients with hyperdiploidy (11/29, 38%) than in those without (3/27, 11%), although the reverse association was seen in MM. They defined ploidy by measuring the plasma cell DNA content using the Feulgen reaction and image cytometry. We are unable to explain this discrepancy although the fact that ploidy was evaluated by two different methods may be partially responsible. Pseudodiploidy and low chromosome count hyperdiploidy (48-49 chromosomes) are potentially difficult to identify by interphase FISH, compared to true hypodiploidy or high chromosome count hyperdiploidy. However, the comparison of our interphase FISH ploidy results with actual karyotypes for those MGUS (n=8) and SMM (n=24) patients with abnormal cytogenetics showed that all cases but one were accurately classified. Thus interphase FISH misclassification of ploidy is unlikely to account for the significant difference in results between the two series.

Abnormalities of 14q32 were observed in the majority of clonal plasma cells, independently of the stage of the disease, whereas the percentages of plasma cells carrying Δ13 or the 16q23 deletion varied significantly between MGUS, SMM and MM, with MGUS patients showing the greatest heterogeneity. In MGUS, Δ13 was often present in a subclone of the abnormal plasma cells. Although low level clones in MGUS may be due to only a small proportion of the CD138-positive plasma cells being part of the neoplastic clone, our results indicate that, in these cases, the Δ13 is a later change following *IgH* translocations or multiple trisomies. Similar findings were observed for most low level 16q23 deletions in which the cells were found to be 100% positive for other chromosomal aberrations.

Our results clearly show that the time of occurrence of specific abnormalities is crucially dependent on genetic context. The t(4;14), t(14;16) and t(14;20) are highly associated with Δ13 in MM.[15,17,20] The same association was observed in MGUS and SMM patients. Moreover, in cases with t(4;14) and t(14;16), *IgH* rearrangement and Δ13 were found in a similar proportion of abnormal cells in the three diagnostic groups, suggesting that Δ13 occurred early in disease pathogenesis. However, a different time of occurrence of Δ13 was observed in relation to t(14;20). In MGUS, Δ13 appeared to originate later than t(14;20). A striking difference between MGUS and MM was seen regarding the association of Δ13 with t(11;14). While in MM 21/53 of t(11;14) cases also showed Δ13, in MGUS only 1/28 of cases with the translocation was associated with Δ13 ($p<0.001$). In MM the median percentage of plasma cells carrying the Δ13 in patients with t(11;14) was 98% while in the only case of MGUS with both t(11;14) and Δ13, all the plasma cells were positive for t(11;14) but only 48% of the plasma cells had Δ13. The translocation t(11;14) has been related to t(6;14) on the basis of a similar biological and clinical behavior.[23] Both translocations directly activate a *cyclin* D family member (*CCND1* and *CCND3*, respectively) and gene expression profiling studies demonstrated that cases carrying either one or the other translocation exhibited dysregulation of similar transcriptional programs showing overlapping gene expression profiles.[23,24] As for t(11;14), Δ13 was not found in the MGUS cases with t(6;14), while it was present in the majority of MM cases with this translocation.

These findings are consistent with those reported by Bochtler *et al.*,[25] who applied an oncogenic tree model to study patients with amyloid light chain amyloidosis, MGUS and MM, in order to detect clustering of chromoso-

mal abnormalities. Patients with amyloidosis and MGUS showed the t(11;14) branch independent of Δ13, while t(4;14), and gain of 1q21 were grouped together with Δ13. In our study, Δ13 occurred less frequently in SMM cases with t(11;14), but not to a degree that was statistically significantly different from the MM group.

Conclusions

In this study, we examined a range of numerical and structural chromosomal changes in MGUS, SMM and MM patients. None of the chromosomal aberrations tested was exclusive to a single diagnostic group, confirming the extensive overlap between the different conditions from a genetic point of view. However, statistically significant differences were observed in the incidence of specific abnormalities between the three conditions, in particular for Δ13, 16q23 deletion and *TP53* deletion. In MGUS, the greatest variation in the proportion of abnormal plasma cells carrying the abnormality was seen for Δ13 and 16q23 deletion. In particular, the temporal appearance of Δ13 was related to the presence of specific concomitant abnormalities: early when t(4;14) or t(14;16) was present, later with t(14;20), and even later with t(11;14) or t(6;14). These data suggest a possible role of Δ13 in the transition from MGUS to MM specifically in cases with t(11;14) or t(6;14).

Authorship and Disclosures

LC designed and performed research, analyzed data and wrote the first draft of the paper; GPD, AHI, EDC, RKMP and DMS performed research; KHO, NCPC and CJH contributed to the analysis of the data; FMR designed and performed research, and analyzed data. All the authors contributed to the final draft of the paper. The authors reported no potential conflicts of interest.

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