Hyperdiploidy Is a Common Finding in Monoclonal Gammopathy of Undetermined Significance and Monosomy 13 Is Restricted to These Hyperdiploid Patients

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Abstract

Purpose: Two pathways, hyperdiploid and nonhyperdiploid, are proposed for progression to plasma cell neoplasia. Implication of monosomy 13 (D13) is unclear in monoclonal gammopathy of undetermined significance (MGUS), and data on DNA content of plasma cells [DNA index (DI)] are rare.

Experimental Design: We ascertained DI in 169 multiple myeloma (MM) and 96 MGUS patients. Interphase fluorescence in situ hybridization (FISH) coupled to cytoplasmic staining of specific Ig (cIg-FISH) was done to look for trisomies and to ascertain D13.

Results: Hyperdiploidy and hypodiploidy were found in 54% and 11.5% of MGUS patients and in 59.5% and 25% of MM patients, respectively. In MGUS patients tested using probes for odd chromosomes, cIg-FISH showed association between trisomies for chromosomes 3, 7, 9, 11, or 15 and hyperdiploidy. D13 was found in 45.3% and 24.6% of MM and MGUS patients, respectively. Most D13 cases observed in MGUS were found within hyperdiploid clones, 38% versus 11% in hypodiploid cases, in sharp contrast with the occurrence of D13 in MM patients, 31.9% and 76.3%, respectively. That peculiar distribution of D13 according to DI persisted with other thresholds used to ascertain hyperdiploidy, such as DI ≥ 1.05. A strong relationship between IgA peak and hypodiploidy (P = 0.007) was only observed in MM, whereas light chain was significantly associated with hypodiploidy in MGUS (P = 0.001) and MM (P = 0.05). Hyperdiploidy shows similar pattern in MGUS and MM.

Conclusion: This fits well a hyperdiploid pathway leading to MM after a preceding MGUS stage. Yet-to-be-determined secondary event(s) needs to occur for the transition to MM, unrelated to changes in chromosome number or to loss of chromosome 13. In contrast, the “nonhyperdiploid” pathway needs to be clarified further because hypodiploidy is less common in MGUS than in MM and D13 is rare in hypodiploid MGUS patients compared with hypodiploid MM patients.

Karyotypes from multiple myeloma (MM) patients are complex but may be categorized either as hyperdiploid, displaying gain of odd chromosomes and some structural changes, or as hypodiploid or pseudodiploid, displaying loss of even chromosomes and frequent structural changes, including IgH rearrangements (1, 2). Interphase fluorescence in situ hybridization (FISH) studies done on large series of MM patients have shown that chromosome changes are observed in almost all MM patients (3) and that monosomy 13 (D13), hypodiploidy, and some IgH translocations are related to adverse prognosis in MM (1, 2, 4–11).

Monoclonal gammopathy of undetermined significance (MGUS) is an indolent condition that can progress to malignant MM at a rate of 0.6% to 3% yearly (12, 13). With some exceptions (14, 15), conventional cytogenetic study is unsuccessful in MGUS, and most information about cytogenetic status has been drawn from interphase FISH studies done on bone marrow plasma cells (BMPC). Numerical chromosome changes are observed in up to 60% (16–19) and IgH translocations in up to 48% of patients tested (9, 18, 20, 21). Several studies have suggested that IgH translocations might occur early in the development of monoclonal gammopathies, possibly as an immortalizing event, rather than related to transition to MM (9–11, 18, 20–22). There is still matter of debate whether D13 is an initiation event or is related to transition to MM due to the variable percentage of MGUS patients displaying that anomaly in literature data (9, 10, 18–23).
Thus far, little is known about the real incidence of hyperdiploidy and hypodiploidy in MGUS due to inability to do conventional cytogenetic study in most instances (14, 15). Flow cytometry (FCM), a good method to ascertain hyperdiploidy in MM patients (24–27), was applied to MGUS patients and, although the number of cases reported was low, showed that some patients showed a hyperdiploid PC clone (24–26, 28, 29). As trisomies for odd chromosomes (with the exception of 13) occur almost exclusively in association with hyperdiploidy (1, 2), interphase FISH techniques showing such changes have been proposed as a surrogate to identify ploidy subtypes in MGUS and found that 11 of 28 MGUS/smoldering MM were certainly hyperdiploid (30).

In this study, we focused on DNA content of PC as determined using Feulgen reaction and image cytometry, a powerful method for the analysis of abnormal cells in small amounts scattered among large numbers of nonmalignant cells (31). We determined DNA index (DI) of PC in 169 MM patients at diagnosis and in 96 MGUS. Interphase FISH (cIg-FISH) using centromeric probes for odd chromosomes was tested to add information about chromosomes changes in part of MGUS patients, and loss of retinoblastoma gene-1 gene was used to ascertain Δ13 in MGUS and MM patients. Data found show that MGUS and MM share the same high number of hyperdiploid cases, in contrast to hypodiploidy, a rare event in MGUS but not in MM. Δ13 was shown less frequently in MGUS than in MM, almost all deleted cases belonging to hyperdiploid MGUS and rarely to hypodiploid MGUS. These new data on DI and Δ13 in MGUS raise several questions about the multistep pathway(s) leading to MM.

### Materials and Methods

#### Patients

BMPCs from eight healthy bone marrow donors (41-45 years old) were studied using the same methods as for MGUS and MM patients after informed and written consent. In each of the eight donors, DI was found between 0.98 and 1.00, and these results were considered as reflecting normal DNA content. Ninety-six patients fulfilling criteria for MGUS (12, 13) were studied at discovery of the monoclonal peak. Each patient was followed for at least 12 months to ascertain stability of the peak (range, 12-132 months; median, 72 months). Nature of the Ig peak from MM patients was as follows: GK (n = 67), GL (n = 36), AK (n = 17), AL (n = 24), DL (n = 2), biclonal (n = 3), Bence Jones λ (n = 12); λ (n = 5); ) or nonsecretory (n = 3). Nature of the Ig peak from MGUS patients was as follows: GK (n = 42), GL (n = 22), AK (n = 12), AL (n = 10), DL (n = 2), biclonal (n = 7), and Bence Jones λ (n = 1). Some results from 18 patients were previously published (32). One hundred and sixty-nine patients fulfilling criteria for MM (13, 33) were analyzed at diagnosis to ascertain DNA content of PC and incidence of Δ13.

#### Methods

In each patient, a bone marrow sample was collected on EDTA anticoagulant after informed and written consent. After mononuclear cell separation (MSL, Eurobio), cells were cyt centrifuged and slides were air dried; slides were either analyzed within 3 days or kept frozen until use.

**DNA content of plasma cells (DI).** Feulgen reaction using pararosanilin as the Schiff reagent was done on cytopsin slides as described previously (31). BMPCs were identified according to their morphology (large cells, low nuclear to cytoplasmic ratio, and eccentric nucleus appearing in red or pink). Stained cells were examined under a microscope coupled with a video camera and a computerized image analyzer (DMRB microscope, Quantimet 600 S image analyzer, both from Leica). DI was calculated as the ratio of the mean absorbance of PC nuclei to the mean absorbance of lymphocyte nuclei from the same slide (see ref. 31 for details).

We used results from a previously published successful conventional cytogenetic analysis done in 57 MM patients (34, 35) for comparison with DNA content analysis done in the same patients.

**Interphase FISH studies.** Among the various probes that may be used to detect aneuploidy in BMPC, we referred to previously published results (16) and to our experience on conventional karyotypes done in MM (34). Among the six chromosomes that were most frequently found as trisomic (or tetrasonic) into hyperdiploid MM karyotypes, we selected chromosomes 3, 7, 9, 11, and 15. To detect numerical abnormalities specifically within PC (cIg-FISH), slides were fixed in acetone and paraformaldehyde and incubated next with fluorescent (FITC)-labeled antihuman light chains and interphase FISH was done next. In 118 patients, biotinylated centromeric DNA probes directed against chromosomes 3, 7, 9, 11, and 15 (D3Z1, D7Z1, D9Z1, D11Z1, D15Z1, and Oncor) and Texas red avidin for the

### Table 1. DNA content of plasma cells using image analysis in MGUS and MM

<table>
<thead>
<tr>
<th>Hypodiploidy</th>
<th>Reference range</th>
<th>Hyperdiploidy</th>
<th>Triploidy or tetraploidy</th>
</tr>
</thead>
<tbody>
<tr>
<td>(0.98-1.00)</td>
<td>(1.01-1.45)</td>
<td>(1.79-2.06)</td>
<td></td>
</tr>
<tr>
<td>MGUS (n = 96)</td>
<td>n = 33 (34.5%)</td>
<td>n = 52 (54%)</td>
<td>n = 0</td>
</tr>
<tr>
<td>Mean, 0.94</td>
<td>Median, 1.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range, 0.86-0.97</td>
<td>Mean, 0.94</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MM (n = 169)</td>
<td>n = 21 (12.5%)</td>
<td>n = 101 (59.5%)</td>
<td>n = 5 (3%)</td>
</tr>
<tr>
<td>Mean, 0.93</td>
<td>Median, 1.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range, 0.80-0.97</td>
<td>Mean, 0.94</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NOTE: A similar percentage of hyperdiploid patients was found in MM and MGUS, whereas hypodiploidy was rare in MGUS. Among the patients showing DI within reference range, interphase FISH showed abnormal number of chromosomes in 6 of 9 MGUS patients tested (see text) and in 10 of 21 MM patients from that group that showed Δ13 (see text).

*Including one patient with two peaks of ploidy (0.86 and 1.00).

† Including nine patients with a diploid clone and a hyperdiploid (1.05-1.18) peak and one patient with two diploid peaks.

‡ Including one patient with two peaks (0.95 and 1.00).

§ Including seven patients with a diploid peak and a hyperdiploid (1.11-1.40) peak.

|||
revelation of hybridization were used as published previously (32). In 24 other patients, we applied a superimposable protocol but using directly labeled probes for the same odd chromosomes (Spectrum Green or Spectrum Orange, Vysis). Thresholds used to ascertain trisomy were those from biotinylated probes (8%; mean ± 3 SD).

The status of chromosome 13q14 was determined using cIg-FISH and the retinoblastoma gene 1 probe (Vysis). Threshold to ascertain Δ13 was 15% (mean ± 3 SD).

Statistics. Comparison between groups was done through Fisher’s exact χ² test. Correlations between numerical variables were tested through Pearson correlation coefficient. All analyses were done using Statistical Package for the Social Sciences software.

Results

DI in monoclonal gammopathies. In MGUS, analysis was done in 96 patients and results are reported in Table 1 and Fig. 1. According to the patients, 62 to 143 BMPCs could be analyzed. In 85 patients (88.5%), only one peak of ploidy was observed (coefficient of variation of <5.6% in 56 patients and <8% in 29 patients in this group). In nine cases (9.5%), two peaks corresponding to a hyperdiploid clone (DI = 1.05-1.18) and to diploid cells were present (percentage of PC displaying hyperdiploidy ranged from 40% to 72% in this group). In one case, two peaks, both hyperdiploid (DI = 1.03 and 1.22), were found (corresponding to 27% and 73% PC analyzed, respectively). In one case, a hypodiploid clone (DI = 0.86; 57% PC were hypodiploid) was observed together with a diploid peak.

In MM, analysis was done in 169 patients (Table 1; Fig. 1). At least 200 PC were analyzed in each case. In nine patients, a few diploid PC (10-22%) was observed: together with a hyperdiploid clone in seven cases (DI = 1.06-1.45), together with a near tetraploid and a tetraploid clone in two cases (DI = 1.96 and 2.00, respectively), and together with a hypodiploid clone in one case (DI = 0.95). In five patients (including the two previously mentioned patients who showed a near tetraploid clone), DI ranged from 1.79 to 2.06: these patients were gathered within one subgroup (hypertetraploid or pseudotetraploid DI).

Hyperdiploidy was observed in 54% of MGUS patients and in 59.5% of MM patients (Table 1). Mean, median, and range of DI were similar in MGUS as in MM (Fig. 1). In contrast, a hypodiploid clone was infrequent in MGUS (11.5% of patients) compared with MM (hypodiploidy in 25% of patients; \( P = 0.006 \)), but range, mean, and median for hypodiploid DI were not different between MM and MGUS patients (Table 1). Normal DI was observed in 34.5% and 12.5% of patients with MGUS and MM, respectively (\( P < 0.001 \); Table 1). However, as described later, some MGUS and MM patients from this so-called “diploid” group showed abnormal findings after cIg-FISH, showing that this group included at least some pseudodiploid cases. Literature data using FCM ascertain hyperdiploidy if DI is ≥1.05. Using this threshold, we found hyperdiploidy in 50% and 39% of MM and MGUS patients, respectively. Comparison was done between DI and modal number of chromosomes from abnormal karyotypes found in 57 MM patients, which showed linear relationship between both variables (Fig. 2).

IgA peak was more frequent in nonhyperdiploid (hypodiploid) MGUS and MM compared with hyperdiploid MGUS and MM patients, respectively, but difference was only significant in MM (\( P = 0.007 \)). In respect to Ig light chain, λ light chain was significantly associated with hypodiploidy (nonhypodiploidy) in MGUS (\( P = 0.001 \)) as well as in MM (\( P = 0.05 \)).

cIg-FISH using centromeric probes and relationship with DI in MGUS patients. BMPCs from 42 MGUS patients were tested (54-123 PC tested in each case) using at least two centromeric probes (3, 7, 9, 11, and 15). Abnormal patterns were observed in 34 patients (81%), corresponding to monosomy 7 in one instance and to trisomy or tetrasomy in all other instances. According to the probes tested, trisomy for chromosomes 3, 7, 9, 11, and 15 could be ascertained in 55%, 42%, 45%, 57%, and 57% of patients, respectively. In some instances, tetrasomy for at least one probe tested was observed in a limited number of PC in each instance (4-48%; mean, 17%).

In patients showing hyperdiploid DI, trisomy for at least one chromosome was observed in 26 of 28 (93%) cases, and trisomy for at least two chromosomes was observed in 21 of 28 (75%) cases. Tetrasomy for at least one chromosome was present in MGUS patients displaying DI > 1.10 (data not shown).
In hypodiploid patients (DI $\leq 0.97$), a small subclone of PC showing trisomy 3 was found in two of five cases tested (11% PC in each case). In patients with DI = 0.98-1.00, six of nine patients showed trisomy for one or two chromosomes in a limited number of PC in each instance (11-55%; mean, 25%).

**Monosomy 13.** $\Delta 13$ was observed in 14 of 57 (24.6%) MGUS patients and in 68 of 150 (45.3%) MM patients tested ($P = 0.03$; Table 2). In MGUS, the number of PC displaying $\Delta 13$ was <50% in six patients (26-48%; mean, 36%) and was >50% in eight patients (59-88%; mean, 76%), whereas in MM the number of PC displaying $\Delta 13$ was <50% in 28% of patients and >50% (50-78%) in 72% of patients, respectively. Trisomy 13 was found in a MM patient who showed DI = 1.79 (interpreted as hypotetraploidy), and two or only one spot for *retinoblastoma gene-1* gene was observed in the two MM patients tested who displayed near tetraploidy.

$\Delta 13$ was observed in 38% of hyperdiploid MGUS patients and in 31.9% of hyperdiploid MM patients (Table 2) but was infrequent in hypodiploid MGUS patients (1 of 9, 11%) compared with hypodiploid MM patients (29 of 39, 76.3%; $P = 0.0001$; Table 2). Using DI $\geq 1.05$ as the threshold, $\Delta 13$ was observed in a superimposable number of hyperdiploid MGUS and hyperdiploid MM patients (32% versus 30%), whereas it was infrequent in nonhyperdiploid MM patients (21%) compared with nonhyperdiploid MM patients (Table 3).

In this series, using either DI or interphase FISH or both, we found overall a cytogenetically abnormal clone in 70 of 96 (73%) MGUS patients.

**Follow-up.** After a median follow-up of 72 months (12-132 months), only two (2%) patients evolved into MM after 88 and 114 months, respectively. Both patients showed a hyperdiploid clone at diagnosis of the MGUS (DI = 1.05 and 1.18), respectively; no $\Delta 13$ was found in each case. No cytogenetic analysis was done at diagnosis of the MM.

### Discussion

In this study, we show a similar incidence of hypodiploid cases together with a similar average DNA in excess and a similar incidence of $\Delta 13$ in MGUS as in MM. In contrast, hypodiploidy (nonhyperdiploidy) is less frequent in MGUS compared with MM, and only a few hypodiploid MGUS show $\Delta 13$ whereas it is a hallmark in hypodiploid MM.

Thus far, FCM has been shown powerful in delineating a hyperdiploid group of 55% to 65% of MM patients (23–27), and we found a percentage of hyperdiploid MM patients within the same range using image cytometry. Relationship between DI and modal number of chromosomes from MM karyotypes obtained after conventional cytogenetic study confirmed the value of image cytometry to determine DI. Whereas FCM is not the method of choice to ascertain hypodiploidy or pseudodiploidy in MM (24–27), it was possible here to define a group of 25% of hypodiploid patients comparable with data from conventional cytogenetic studies (1, 2, 14).

In MGUS, literature data have reported that some MGUS patients show a hyperdiploid clone after FCM study, DI being as high as 1.61 (24, 27–29). In our series, we observed that a large number (54%) of MGUS patients displayed a hyperdiploid clone. That number was superimposable to that found in MM (59%), and the mean amount of DNA in excess for individual patients was similar in MGUS as in MM. Applying the threshold from FCM (DI $\geq 1.05$) to ascertain hyperdiploidy, we found that 50% of MM patients and 39% of MGUS patients fulfilled that definition for hyperdiploidy. Using cIg-FISH, the exhibition of trisomies for odd chromosomes was proposed recently to identify hyperdiploid patients in monoclonal gammopathies (31, 36). We also found here that trisomy for at least one among chromosomes 3, 7, 9, 11, and 15 was present in many hyperdiploid MGUS patients as determined using image cytometry. We observed that median hyperdiploid DI was as high in MGUS as in MM, hypothesizing that there is no threshold for DI over or under which malignancy occurs and that several cytogenetic changes, at least numerical, are already established in hyperdiploid MGUS patients. We and others have previously shown that chromosome instability was not infrequent in hyperdiploid PC clones from MGUS patients, although they did not evolve to MM (19, 32). Qualitative (yet to be determined) rather than

### Table 2. $\Delta 13$, as determined using cIg-FISH and loss of *retinoblastoma gene-1* gene, in MGUS and MM patients

<table>
<thead>
<tr>
<th></th>
<th>All, no. patients (%)</th>
<th>Hypodiploidy, no. patients (%)</th>
<th>Diploidy, no. patients (%)</th>
<th>Hyperdiploidy, no. patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGUS</td>
<td>14/57 (24.6)</td>
<td>1/9 (11.1)</td>
<td>2/18 (11.1)</td>
<td>11/29 (38)</td>
</tr>
<tr>
<td>MM</td>
<td>68/150 (45.3)</td>
<td>29/38 (76.3)</td>
<td>10/21 (47.6)</td>
<td>29/91 (31.9)</td>
</tr>
</tbody>
</table>

### Table 3. Distribution of $\Delta 13$ according to ploidy using thresholds derived from image cytometry or from FCM

<table>
<thead>
<tr>
<th></th>
<th>Hyperdiploidy</th>
<th>Nonhyperdiploidy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutoff</td>
<td>DI &gt; 1.00</td>
<td>DI $\geq 1.05$</td>
</tr>
<tr>
<td>MGUS</td>
<td>11/29 (38%)</td>
<td>6/19 (32%)</td>
</tr>
<tr>
<td>MM</td>
<td>29/91 (32%)</td>
<td>24/80 (30%)</td>
</tr>
</tbody>
</table>

NOTE: Independently of the threshold used for the definition of hyperdiploidy, $\Delta 13$ was observed in a similar number of MM and MGUS patients. In contrast, whatever the threshold used for the definition of hypodiploidy (nonhyperdiploidy), $\Delta 13$ was rare in MGUS and frequent in MM patients.
quantitative changes are therefore stressed for the transition from hyperdiploid MGUS to MM.

There is no report on the incidence of hypodiploidy in MGUS due to technical limitations of FCM as mentioned above. We observed that hypodiploid patients were rare in MGUS compared with MM. If we cannot exclude that polyclonal PC persisting in MGUS patients might have masqueraded small aneuploid (hypodiploid) clones in some instances, leading to underestimate the percentage of hypodiploid cases, mean and median for hypodiploid DI for these few hypodiploid MGUS patients were similar to that found for MM patients. Out of Δ13 (discussed later), there is no cytogenetic study or clq-FISH done in MGUS, which is able to delineate hypodiploid cases.

Looking for Δ13 in MM patients, we found an incidence superimposable to that reported by most groups (~50%; refs. 1, 2, 4–6, 9, 18) and also that Δ13 was much more frequent in the hypodiploid than the hyperdiploid MM patients (1, 2, 36). We found Δ13 in 24.6% of MGUS patients. Some authors showed the same high incidence of Δ13 in MGUS as in MM (~50%) and proposed Δ13 as an early event not associated with evolution into MM (21–23). Other authors found a lower percentage (20–25%) compared with MM, which might indicate that Δ13 is a late event related to the transition to MM (18, 20). Discrepancies on incidence of Δ13 according to the series (18, 20–23) might be related to the relative amount of hypodiploid and hyperdiploid patients in each cohort of patients tested. In our series, Δ13 was rare in hypodiploid MGUS (11%) in contrast to hypodiploid MM (76%). Using another threshold for ploidy (DI ≥ 1.05 to ascertain hyperdiploidy) confirmed similar incidence of Δ13 in hyperdiploid MGUS and hyperdiploid MM and its low frequency in nonhyperdiploid MGUS compared with MM. We observed that average amount of DNA lost was similar in hypodiploid MM as in hypodiploid MGUS (similar DI), which might indicate that if some (several) chromosome changes already occurred, at least chromosome 13 was infrequently involved in the process.

Δ13 is lost in many MM patients and might not bear the same significance if observed in hypodiploid or hyperdiploid MM karyotypes (1, 2). Δ13 might also differ if discovered within a hyperdiploid or within a hypodiploid PC clone observed in MGUS. Considering hyperdiploid MGUS, Δ13 might be one among the several chromosome changes involving odd chromosomes and related to an event (32) without relationship with transformation into MM. Occurrence of Δ13 in hypodiploid MGUS might be a late event, possibly related to transition to MM. However, we cannot exclude that hypodiploidy is rare in MGUS because hypodiploid MM originates rarely from a preceding MGUS condition.

IgH rearrangements account for up to 70% of MM patients and 50% of MGUS patients (8, 9, 15, 18, 20) and have been proposed as the primary event in the process leading to MM (10, 11, 22, 36). Using image cytometry and clq-FISH, 73% of MGUS patients showed chromosome changes, a percentage higher than that related to IgH translocations. So, if the very early changes occurring within the germinal center B cell might be related to IgH rearrangements, they might be at times related first to numerical chromosome changes as recently hypothesized (10). If two pathways were proposed for progression to plasma cell neoplasia, one hypodiploid and one hyperdiploid (10, 11, 36, 37), we observed here that many MGUS patients were clearly driven into a hyperdiploid pathway, whereas it was not so clear-cut considering hypodiploid patients. Chromosomal changes seem to be not far from fully established in hyperdiploid MGUS but are insufficient to induce overt malignancy (19, 32), suggesting that other changes (molecular and epigenetic) might drive for the transition to MM (10, 11, 22).

It is also in agreement with results from microarray expression analysis, which shows that differences between MGUS and MM are smaller than those between normal and MM or normal and MGUS (38). Very few patients from this series evolved to MM after a median follow-up of 72 months, and it is not possible to draw conclusions about relationship between DI and prognosis in MGUS. However, we observed that IgA and λ light chain were more frequent in hypodiploid MGUS cases. Further delineation of “nonhypodiploidy” in MGUS will certainly help us to understand better the origin of MM.

Acknowledgments

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Hyperdiploidy and Monosomy 13 in MGUS


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