Optical genome mapping reveals complex cytogenetic abnormalities in multiple myeloma

Multiple myeloma (MM) and its aggressive form, plasma cell leukemia (PCL), are hematologic neoplasms characterized by pathological clones of antibody-secreting plasma cells.[1] Currently, next-generation sequencing (NGS) and conventional cytogenetic methods (e.g., karyotyping and fluorescence *in situ* hybridization [FISH]) are commonly used to identify genetic abnormalities that influence risk stratification.[2,3] However, NGS focuses on detecting variants in the DNA sequence, whereas both karyotyping and FISH are limited in resolution and scope, hindering a comprehensive analysis of the cytogenetic landscape in MM.

Recent research highlights the need for better characterization of malignant plasma cells to refine diagnosis, prognosis, and treatment.[4] High-resolution techniques such as optical genome mapping (OGM) offer a more comprehensive approach, enabling genome-wide detection of structural variants and copy number variations.[5,6]

In this study, OGM, FISH, and karyotyping were employed to analyze chromosomal alterations in a cohort of 21 patients with MM and three with PCL, alongside NGS for gene mutation analysis. We propose that OGM represents a valuable tool for characterizing the cytogenetic complexity of plasma cells in MM by detecting recurrent, complex, and novel structural alterations with potential prognostic and therapeutic relevance in MM and PCL.

All patients were diagnosed between January 2024 and January 2025 at Hospital Universitario Virgen de las Nieves (Granada, Spain) and met the diagnostic criteria defined by the International Myeloma Working Group.[7] MM patients had ≥30% clonal plasma cells in bone marrow, and PCL patients had ≥30% in peripheral blood. The patients' clinical data are summarized in Table 1. All patients gave written informed consent, and the study complied with the Declaration of Helsinki.

OGM was performed on fresh bone marrow or peripheral blood without prior CD138$^+$ cell purification, following Bionano protocols, and analyzed using Bionano Access v1.8 with the Rare Variant Analysis algorithm and the GRCh38 reference genome. NGS was carried out with a 43-gene panel (Sophia Genetics) on an Illumina MiSeq (V3 600-cycle), using DDM software and aligned to GRCh37/hg19. For FISH, CD138$^+$ plasma cells were isolated (autoMACS Pro, Miltenyi Biotec) with >96% purity confirmed by flow cytometry, and key MM alterations were assessed using commercial probes (Metasystems). Conventional karyotyping was performed externally in 16 patients. Of these cases, four had no metaphase growth, eight showed normal karyotypes but revealed structural and numerical abnormalities by OGM, and four exhibited complex karyotypes (Table 1), with OGM offering a more precise characterization, including detection of a cryptic high-risk t(4;14) in one case (*Online Supplementary Figure S1A, Online Supplementary Table S1*).

FISH was performed in 22 patients, detecting cytogenetic alterations in 12 (54.5%), while ten (45.5%) showed no abnormalities. All FISH results were fully concordant with OGM findings (Table 1). However, OGM identified additional chromosomal abnormalities, allowing classification into four levels of cytogenetic complexity. Three patients had normal profiles, with no significant structural variants or copy number variations. Five showed non-complex profiles (≤3 structural variants/copy number variations) (Figure 1A). Eleven exhibited complex profiles (4 to 15 structural variants/copy number variations), including four with hyperdiploidy (Figure 1B), three with standard-risk translocations, such as t(6;14) and t(11;14), and four, two of them with PCL, with high-risk alterations involving chromosome 1 or t(4;14). Finally, five patients, including one with PCL, had highly complex profiles, characterized by more than 15 structural variants/copy number variations and evidence of chromoanagenesis (Figure 1C). Among these, three patients with MM and one with PCL carried del(17p) with *TP53* loss, in all cases associated with aggressive or progressive disease. Notably, one MM patient showed extensive chromoanagenesis affecting up to 11 chromosomes but no *TP53* alterations; the only high-risk lesion in this case was a 1q21 gain.

Additionally, we analyzed cytogenetic complexity in one patient at baseline (Figure 2A) and at relapse 6 months later (Figure 2B). At diagnosis, the patient showed a non-complex profile with three chromosomal rearrangements of uncertain significance. Upon progression, the profile became highly complex, with high-risk alterations including 1q21 gain and 17p deletion (Table 1). Alterations present at diagnosis persisted during disease progression, except for a t(8;11) translocation (*Online Supplementary Table S1*).

OGM revealed additional structural variants of uncertain significance, including deletions, insertions, duplications, inversions, and translocations, whose number correlated with cytogenetic complexity, averaging ten in those with normal profiles, 16 in those with non-complex profiles, 27 in those with complex profiles, and 57 in those with highly complex profiles. Several structural variants involved genes not previously linked to MM but associated with other malignancies. Notably, one patient exhibited a t(X;5) translocation resulting in a *DDX4*::*MAP3K15* fusion, potentially relevant to MM pathogenesis given the role of these genes in cell cycle regulation and tumorigenesis, although functional validation is required (*Online Supplementary Table S1*).

Moreover, NGS was performed in 21 patients to detect vari-

Table 1. Clinical data and summary of results from next-generation sequencing, karyotyping, fluorescence *in situ* hybridization and optical genome mapping.

MM patient	Sex	Age years	Diagnosis	PC %[a]	NGS mutated gene (VAF %)	Karyotype	FISH[b]	OGM HR alteration[c] Cytogenetic profile[d]
1	M	75	κ IgA	40	T*ENT5C* (2)	NA	Normal	No HR alterations Normal profile
2	F	59	κ IgA	30	NA	No dividing cells	Normal	No HR alterations Normal profile
3	M	65	κ IgG	31	ND	Normal	Normal	No HR alterations Normal profile
4	F	47	λ IgG	33	*ZFHX4* (23) *KRAS* (5) *NRAS* (3)	Normal	Normal	No HR alterations Non-complex profile
5	M	73	κ IgG	31	*CYLD* (8) *ZFHX4* (7) *FAT3* (7)	NA	Normal	No HR alterations Non-complex profile
6	M	70	Progressing λ IgA	49	NA	No dividing cells	1q21 gain	1q21 gain Non-complex profile
7	M	82	κ IgA	60	*DUSP2* (18)	NA	1q21 gain,	1q21 gain Non-complex profile
8	M	75	κ IgG	44	*TRAF3* (5) *KRAS* (4)	Normal	1p32 deletion 1q21 gain	1p32 deletion, 1q21 gain Non-complex profile
9	M	78	λ FLC	90	*NRAS* (13)	No dividing cells	Normal	No HR alterations Complex profile
10	M	56	κ IgG	32	*NRAS* (7)	Normal	Normal	No HR alterations Complex profile (hyperdiploidy)
11	M	45	κ IgG	95	ND	Normal	Normal	No HR alterations Complex profile (hyperdiploidy)
12	M	56	λ FLC	76	*TRAF3* (13) *LTB* (11)	Complex	Normal	No HR alterations Complex profile (hyperdiploidy)
13	M	87	κ IgA	33	*KRAS* (13)	NA	Normal	No HR alterations Complex profile (hyperdiploidy)
14	F	77	λ IgG	70	*KRAS* (36) *NRAS* (46)	Normal	*CCND1::IGH*	No HR alterations, Complex profile (chromoanagenesis, *CCND1::IGH*)
15	M	66	κ IgG	32	NA	Normal	1p32 deletion	1p32 deletion Complex profile
16	M	64	κ IgA	30	*TP53* (24) *CCND1* (31)	NA	1q21 gain *CCND1::IGH*	1q21 gain Complex profile (*CCND1::IGH*)
17	M	64	λ IgG	30	ND	NA	1p32 deletion 1q21 gain	1p32 deletion, 1q21 gain. Complex profile.
18	M	79	λ IgA	81	*KRAS* (19)	NA	1q21 gain *CCND1::IGH*	1q21 gain, Highly complex profile (chromoanagenesis, *CCND1::IGH*)

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MM patient	Sex	Age years	Diagnosis	PC %[a]	NGS mutated gene (VAF %)	Karyotype	FISH[b]	OGM HR alteration[c] Cytogenetic profile[d]
19	M	76	Progressing λ IgA	70	*TP53* (8)	No dividing cells	NA	17p deletion Highly complex profile (chromoanagenesis)
20	M	49	Progressing λ IgG	96	*TP53* (86) *ZFHX4* (44)	Normal	1p32 deletion 1q21 gain 17p deletion	1p32 deletion, 1q21 gain 17p deletion. Highly complex profile (hyperdiploidy and chromoanagenesis)
21[e]	M	63	Basal κ IgA	60	*NRAS* (4)	NA	Normal	No HR alterations Non-complex profile
21[f]	M	63	Progressing κ IgA	35	*NRAS* (27) *RB1* (33)	Complex	1q21 gain 17p deletion	1q21 gain, 17p deletion Highly complex profile
PCL patient	**Sex**	**Age years**	**Diagnosis**	**PC %[a]**	**NGS mutated gene (VAF %)**	**Karyotype**	**FISH[b]**	**OGM HR alteration[c] Cytogenetic profile[d]**
22	M	36	*De novo* κ IgG	80	*DIS3* (39) *CYLD* (25) *KRAS* (7) *KRAS* (5) *BRAF* (4)	NA	1q21 gain	1q21 gain. Complex profile
23	F	63	Progressing λ IgG	43	ND	Complex	1q21 gain *FGFR3::IGH*	1q21 gain, *FGFR3::IGH* Complex profile.
24	M	73	Progressing λ FLC	60	*TP53* (64) *KRAS* (38) *TENT5C* (15)	Normal	NA	1p32 deletion, 17p deletion. Highly complex profile (chromoanagenesis)

[a]Percentage of plasma cells observed in the morphological study of bone marrow aspirate (multiple myeloma) or peripheral blood (plasma cell leukemia). [b]In the fluorescence *in situ* hybridization study, probes were used to analyze recurrent and/or clinically relevant alterations: t(4;14), *FGFR3::IGH*; t(11;14), *CCND1::IGH*; and t(14;16), *IGH::MAF*; as well as 17p13 deletion (*TP53*), 1p32 deletion (*CDKN2C*), and 1q21 gain (*CKS1B*). [c]High-risk chromosomal anomalies: t(4;14), t(14;16), t(14;20), 1q21 gain, 1p32 deletion, and 17p deletion. [d]Classification of the cytogenetic profile: normal (no significant stuctural variants [SV] or copy number variations [CNV] detected), non-complex (≤3 SV/CNV detected), complex (4-15 SV/CNV detected), highly complex (>15 SV/CNV detected with or without the presence of chromoanagenesis). [e,f]Results from the same patient with κ IgA multiple myeloma (patient #21) obtained at baseline (e) and at the time of progression 6 months later (f). MM: multiple myeloma; PC: plasma cell; NGS: next-generation sequencing; VAF: variant allele frequency; FISH: fluorescence *in situ* hybridization; OGM: optical genome mapping; HR: high-risk; M: male; NA: not available; F: female; PCL: plasma cell leukemia; ND: not detected. FLC: free light chains.

ants in 43 MM-related genes. No mutations were identified in four patients, including one with PCL. In the remaining 17, a total of 33 variants were detected across 14 genes, with the most frequently mutated being *KRAS* (N=8), *NRAS* (N=6), *TP53* (N=4), and *ZFHX4* (N=3), all associated with aggressive disease (Table 1). No clear association was observed between overall mutational burden and cytogenetic complexity, except for *TP53* mutations, which were mainly found in patients with complex or highly complex profiles. These *TP53* alterations frequently co-occurred with 17p deletions, resulting in biallelic inactivation, a known marker of poor prognosis and increased risk of relapse.

Our study analyzed cytogenetic profiles of 21 MM and three PCL patients with ≥30% pathological plasma cells using OGM, comparing results with FISH and karyotyping. OGM revealed substantial genetic complexity, identifying both well-established MM-associated alterations and novel structural abnormalities of uncertain clinical significance. Currently, karyotyping, FISH, and NGS are routinely used for diagnosis and risk stratification, in accordance with international guidelines.[1,8] However, FISH is targeted and does not capture overall genetic complexity, while karyotyping is often uninformative, yielding results in only 30% of cases.[9] In contrast, OGM provided a more precise cytogenetic profile by accurately identifying affected chromosomal regions. Limitations of OGM include difficulty in detecting translocations involving entire chromosomal arms (e.g., 1q) when breakpoints lie in heterochromatic, highly repetitive regions (*Online Supplementary Figure S1*).[10] Importantly, OGM identified the cryptic high-risk t(4;14) not visible by karyotyping, highlighting its value in uncovering hidden alterations that can reclassify patients into high-risk groups. Our results were fully consistent with FISH for clinically relevant chromosomal alterations, but OGM identified ad-

ditional copy number variations and structural variants in all cases. While OGM provides more detailed information, there is no consensus on thresholds defining complex genomic profiles.[11] In B-cell chronic lymphocytic leukemia, a threshold of ten anomalies has been suggested to define highly complex cases, but larger cohort studies are needed to standardize criteria of genetic complexity.[12] In our study, OGM allowed us to distinguish different levels of genomic

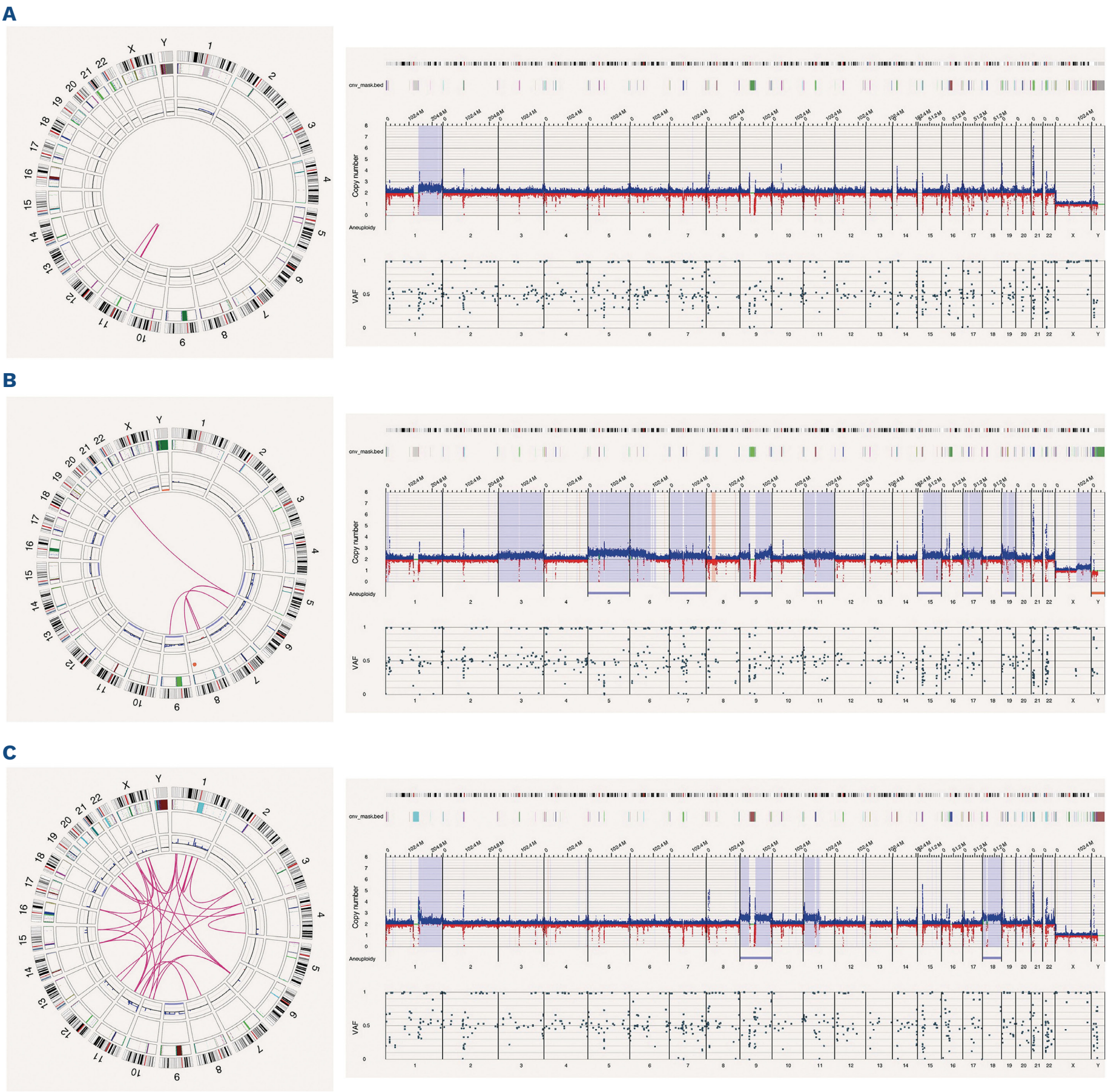

Figure 1. Optical genome mapping results illustrating different cytogenetic complexity profiles. (A-C) Left: circos plot; right: whole genome. (A) Patient #7 with a non-complex cytogenetic profile (≤3 structual variants [SV]/copy number variations [CNV] detected), showing 1q gain as the only high-risk alteration. (B) Patient #13 with a complex profile (4–15 SV/CNV detected), characterized by hyperdiploidy (trisomies of chromosomes 3, 5, 7, 9, 11, 15, 17, and 19), with no high-risk alterations identified. (C) Patient #18 with a highly complex profile (>15 SV/CNV detected), displaying multiple rearrangements affecting nearly all chromosomes, indicative of chromoanagenesis. High-risk 1q gain was detected, along with standard-risk alterations such as the t(11;14) translocation. SV <1 Mb were filtered out from the circos plot unless involving clinically significant regions. The whole genome view enables visualization of CNV in the analyzed sample (gains in blue and losses in red)

complexity based on the number of anomalies detected. No clear association was found between low complexity and favorable outcomes, highlighting the need for larger cohorts to better characterize these patients. In patients with complex and highly complex genomic profiles, OGM provided more accurate detection of genetic alterations, revealing patterns of hyperdiploidy and chromoanagenesis, which are difficult to detect fully with conventional cytogenetic methods. Hyperdiploidy, found in 50-60% of MM cases, involves trisomies of odd-numbered chromosomes and is linked to better treatment response and prognosis.[13] However, it is not routinely assessed due to the need for multiple FISH probes. Our study showed that OGM reliably identified hyperdiploid cases, providing more precise characterization than that afforded by standard methods and highlighting its potential for clinical use and improved assessment of prognostic value of hyperdiploidy.

Chromoanagenesis is characterized by multiple catastrophic events, including complex chromosomal rearrangements and copy number alterations, which may affect a few or several chromosomes.[14] OGM technology has provided deeper insights into this phenomenon in hematologic neoplasms,[11,15] highlighting its potential as a marker of a poor prognosis. In our study, OGM detailed extensive chromosomal rearrangements in patients with chromoanagenesis. Three cases showing biallelic inactivation of *TP53* due to a gene mutation and 17p deletion. In contrast, a fourth patient with a complex profile but without evidence of chromoanagenesis, showed only the 17p deletion. These findings suggest that a double hit on *TP53* may be required to promote the accumulation of complex chromosomal rearrangements, aligning with the hypothesis recently proposed in a study of chromoanagenesis in patients with acute myeloid leukemia.[16] Given this, further studies are necessary to better understand the mechanisms underlying chromoanagenesis, its relationship with *TP53* status, and its impact on disease progression. In this context, OGM proves to be the most effective tool for investigating this complex cytogenetic phenomenon.

Our study included three patients with PCL: two in ad-

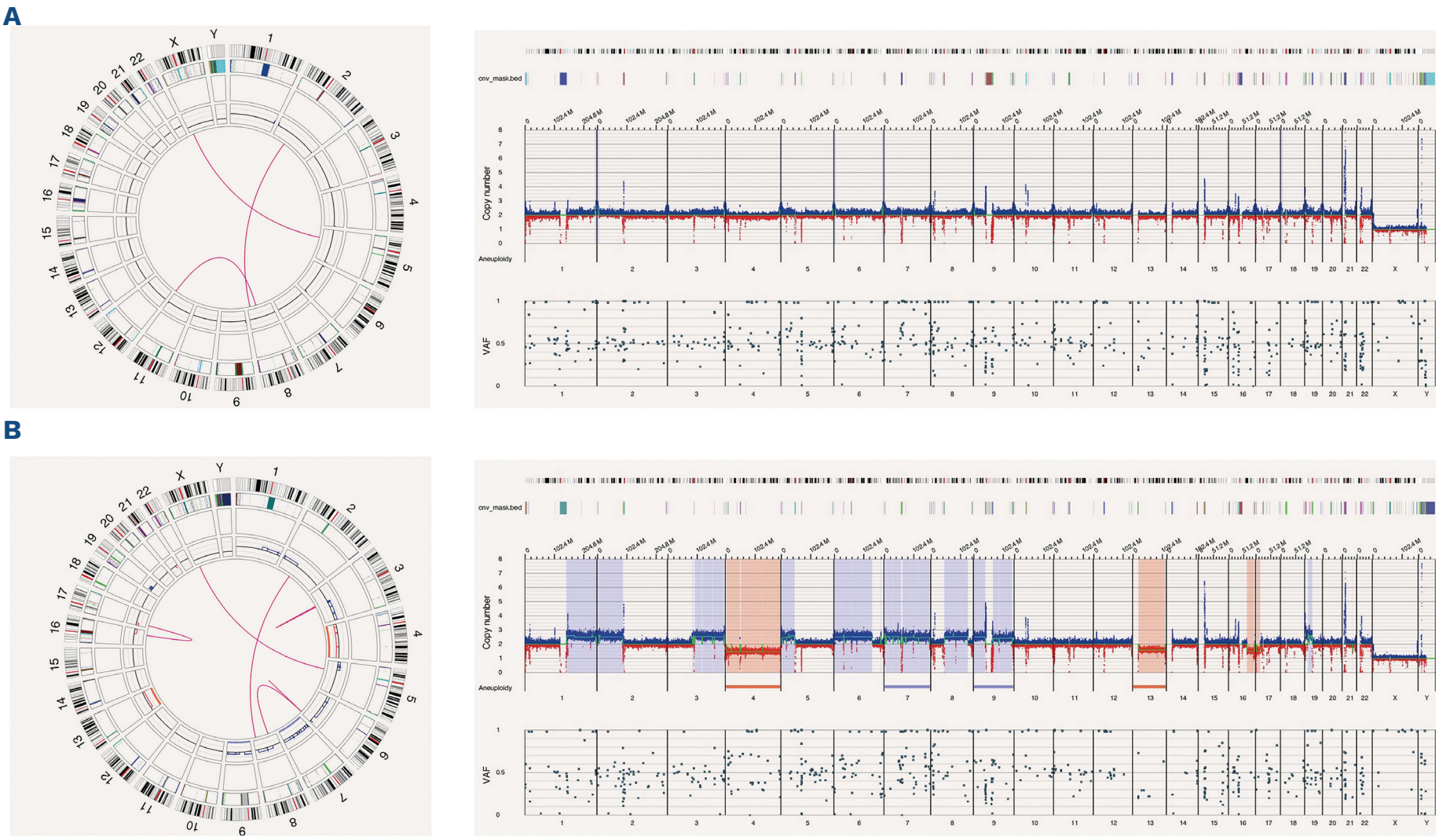

Figure 2. Optical genome mapping reveals the acquisition of chromosomal alterations during disease progression in patient #21. (A, B) Left: circos plot; right: whole genome. (A) Chromosomal alterations detected at the time of diagnosis. (B) Chromosomal profile during disease progression 6 months later. At diagnosis (A), a non-complex cytogenetic profile was observed, characterized by a translocation between chromosomes X and 5 along with subclonal alterations involving translocations between chromosomes 2 and 8 and between chromosomes 8 and 11. At disease progression (B), a highly complex cytogenetic profile was detected, marked by the acquisition of high-risk alterations, including a 1q21 gain and 17p deletion. Additional abnormalities included trisomies of chromosomes 7 and 9; monosomies of chromosomes 4 and 13; gains in regions of chromosomes 2, 3, 5, 6, 8, and 19; a deletion in the long arm of chromosome 16; and translocations between chromosomes 6 and 8 and between chromosomes 16 and 17, the latter associated with 17p loss. Previously identified alterations were still detectable: the t(X;5) and the t(2;8). In contrast, the t(8;11) translocation detected at diagnosis was no longer present, suggesting the regression of a minor cellular subclone.

vanced disease stages and one diagnosed *de novo* (Table 1). All showed complex or highly complex cytogenetic profiles with high-risk alterations typical of PCL. Notably, one case exhibited chromoanagenesis with biallelic *TP53* inactivation. However, larger cohorts are needed to precisely characterize the cytogenetic profile of this aggressive form of disease. Additionally, we used OGM to analyze chromosomal alterations in a MM patient at diagnosis and relapse, observing a shift from a non-complex to a highly complex profile with acquisition of 17p deletion and 1q21 gain. We also observed the loss of an unreported t(8;11) at relapse, possibly reflecting sucblonal regression. MM is characterized by genetically distinct subclones that respond independently to treatment and contribute to disease progression.[17] OGM detects structural variants beyond known high-risk alterations, which could aid in capturing subclonal dynamics. However, its sensitivity is limited, and further studies are needed to clarify the role of OGM in disease monitoring and its potential clinical relevance.

This study revealed numerous structural variants of uncertain significance, whose biological relevance remains unclear. Ongoing analyses using advanced bioinformatic tools aim to assess their recurrence and potential clinical impact.

NGS proved valuable for identifying mutations in genes that may serve as novel therapeutic targets in MM and support patients' enrollment in clinical trials.[18] Importantly, NGS detects mutations in *TP53*, a key high-risk gene, enabling a more complete assessment of biallelic inactivation. Unlike FISH, which only detects 17p deletions, NGS reveals point mutations and small indels. Thus, integrating NGS with cytogenetic analyses provides critical molecular insights that influence prognosis and guide targeted therapies.

This study has some limitations, including the lack of external validation for additional alterations and the small cohort size. Additionally, patients with ≥30% pathological plasma cell infiltration were selected to ensure a homogeneous group and sufficient tumor burden, as OGM has limited sensitivity for copy number variations. To clarify whether these findings extend to cases with a lesser degree of infiltration, OGM is now being applied to purified CD138$^+$ plasma cells, aiming to improve genomic characterization in patients with low tumor burden or at the transition from monoclonal gammopathy of undetermined significance to MM.

In conclusion, OGM may play a key role in unraveling the cytogenetic complexity of plasma cells and capturing their unique genomic "fingerprint". Combined with NGS, it significantly enhances MM genetic characterization by enabling the detection of both structural and sequence-level alterations. This integrated approach improves the identification of high-risk features such as biallelic *TP53* inactivation, hyperdiploidy, and chromoanagenesis. While the MM genomic landscape remains incompletely defined, these technologies are expected to improve diagnosis, risk stratification, and treatment decisions.

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Disclosures

No conflicts of interest to disclose..

Contributions

PJ, JFG-B, MCB-A, LB, TR and MJO-D collected clinical data, performed and reviewed the diagnostic laboratory tests, and selected the cases included in the study. PG performed the FISH analyses. MB, JAP, and JRV conducted the OGM and NGS analyses. JAP and MB analyzed the data, drafted the manuscript, and prepared the table and figures. PJ and JRV contributed to the final revision of the manuscript. FR-C designed the study, supervised the project, and critically reviewed the manuscript. This work was carried out as part of JAP's doctoral thesis.

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Data-sharing statement

Data are available upon reasonable request to the corresponding author.

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