

## CORRESPONDENCE OPEN



# Del(1p32) is an early and high-risk event in multiple myeloma patients with extraosseous disease

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Dear Editor,

Considerable discussion surrounds the prognostic relevance of chromosome 1 aberrations in multiple myeloma (MM), from which most important are gains of 1q21 region and deletions of 1p32 locus [1]. Approximately 10–40% of MM patients develop extraosseous disease (EMM), where plasma cells outside of the bone marrow form tumors called plasmacytomas. Patients with EMM found at disease onset (primary EMM) represent a challenge due to a high risk of relapse and shorter survival. Patients developing plasmacytomas during therapy (secondary EMM) often experience an aggressive disease course, characterized by treatment resistance and early mortality. The exact mechanism of EMM development is not well known, but acquiring genetic alterations is one of the important hallmarks in clonal evolution, leading to EMM spread [2, 3]. Thus, we conducted a detailed evaluation of the distribution and clonal heterogeneity of chromosome 1 aberrations using paired samples from bone marrow and plasmacytoma tissue plasma cells. To assess the broader applicability of our findings, we performed a population-based cytogenetic analysis encompassing both EMM patients and a control cohort of MM patients without a history of EMM.

In twenty-two MM patients, who were diagnosed with EMM between 2022 and 2024 at the University Hospital Brno, a paired sampling of sorted bone marrow plasma cells (BMPCs) and plasmacytoma tissue plasma cells (TPCs) was performed. The interphase fluorescent in situ hybridization (I-FISH) analyses of commonly found aberrations were performed on sorted BMPCs or imprints of plasmacytoma tissue plasma cells (TPCs). Population cytogenetic data of EMM patients treated at the same site between 2015 and 2024 were retrospectively analyzed. During this period, a total of 1020 newly diagnosed multiple myeloma (NDMM) patients were identified at our institution. Among them, 16.3% (167/1020) of patients had a clear presence of EMM (primary EMM in 66.5% (111/167) and secondary EMM was identified in 33.5% of them (56/167)). For comparison, 243 NDMM patients without a history of EMM and with available cytogenetic data were used. Cytogenetics, clinical, and survival data of all primary EMM and control NDMM patients were evaluated from the time of diagnosis. For secondary EMM patients, data were evaluated from the onset of extraosseous plasmacytoma development. To present the cytogenetic findings, we organized them into two main categories reflecting key events in MM pathogenesis: primary events, which include hyperdiploidy (characterized by two or more trisomies of odd chromosomes) and translocations involving the IGH gene, and secondary events, which involve aberrations in chromosomes 1, 13, and 17 [4].

Description of patients' selection, methods, and statistical analysis is provided in a Supplementary data file.

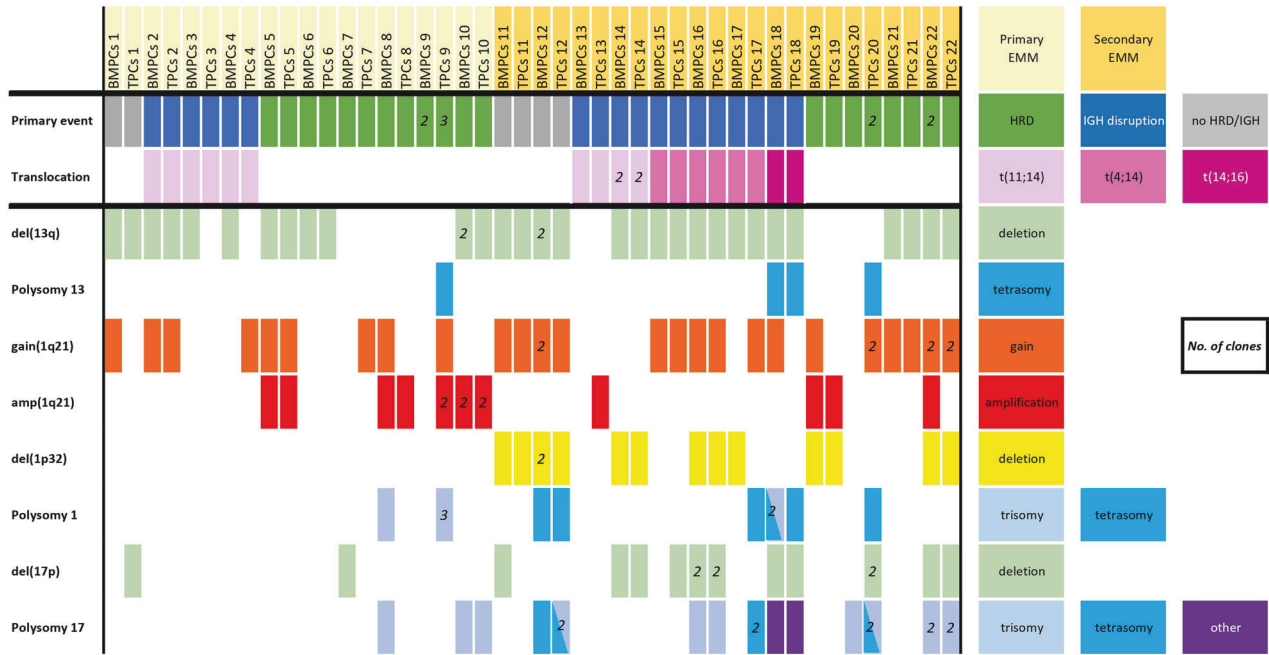
In total, we assessed paired BMPCs and TPCs samples from 10 primary EMM and 12 secondary EMM cases. In all patients, as

expected, the primary events were always shared between BMPCs and TPCs. Del(13q14)/monosomy of 13 was found in 72.7% (16/22) of patients and shared in 87.5% (14/16) of cases. Del(17p)/monosomy of 17 was found in 40.9% (9/22) of patients and it was shared in 44.4% (4/9) of cases. We found chromosome 1 aberrations in 90.9% (20/22) of EMM patients, more often in TPCs than BMPCs (86.4% (19/22) vs 68.2% (15/22)). Only 35.0% (7/20) of patients shared the same 1q21 aberrations between BMPCs and TPCs. The 1q21 aberrations present only in TPCs were found in 30.0% (6/20) of patients. The del(1p32) was in 31.8% (7/22) of patients, in 85.7% (6/7) cases shared between BMPCs and TPCs. We found del(1p32) exclusively in samples from secondary EMM patients. In 71.4% (5/7) of cases, del(1p32) was associated with 1q21 gains. All chromosomal aberrations in patients' BMPCs and TPCs are shown in Fig. 1. Plasmacytoma sites, survival, and other clinical characteristic of those patients are presented in Supplementary Fig. 1 and Supplementary Table 1. Fluorescence microscopy images of BMPC and TPC sub-clones are presented in Supplementary Fig. 2.

Evaluating the population cytogenetic data among patients with primary EMM, secondary EMM, and a control group of NDMM patients without EMM, we found a significant difference in the distribution of del(1p32). A higher proportion of del(1p32) was found in EMM patients, particularly among those with secondary EMM (20.7% (23/111) vs. 28.6% (16/56) vs. 11.1% (27/243);  $p = 0.002$ ). Interestingly, in EMM patients, del(1p32) was significantly associated with 1q21 gains (12.6% (14/111) vs. 25.0% (14/56) vs. 6.2% (15/243);  $p < 0.001$ ). The difference in the proportion of del(1p32) or del(1p32) with 1q21 gains was higher in secondary EMM but did not reach statistical significance (del(1p32) (28.6% (16/56) vs. 20.7% (23/111);  $p = 0.33$ ) and del(1p32) + 1q21 gains (87.5% (14/16) vs. 60.9% (14/23);  $p = 0.086$ )). Furthermore, in secondary EMM patients, del(1p32) was more frequently observed in those with plasmacytoma found in soft tissues (extramedullary type, EMD) compared to those with plasmacytomas arising from the bone lesions (paraneoplastic type, PS) (50.0% (8/16) vs. 20.0% (8/40);  $p = 0.046$ ). Cytogenetics aberrations in all patients' groups are summarized in Table 1.

Thus, we evaluated the survival of EMM patients in the context of del(1p32) and 1q21 gains. For primary EMM patients with both del(1p32) and 1q21 gains, the median PFS was significantly reduced to 7.9 months (95% CI: 3.4–NA), compared to 16.6 months (95% CI: 10.8–NA) in patients with only del(1p32), and 40.2 months (95% CI: 21.9–NA) in patients without either aberration ( $p = 0.003$ ). The median OS for patients with both del(1p32) and 1q21 gains was also significantly reduced, to 10.6 months (95% CI: 8.3–NA), compared to 28.0 months (95% CI: 22.7–NA) and 69.4 months (95% CI: 45.5–NA), respectively ( $p = 0.03$ ). In secondary EMM patients with both del(1p32) and 1q21 gains, the median PFS was significantly shorter at 2.0 months (95% CI: 1.5–5.3), compared to 0.5 months (95% CI: 0.4–NA) in patients with only del(1p32) and 6.6 months (95% CI: 4.8–17.2) in patients without either aberration ( $p < 0.001$ ). Similarly, a significant reduction in median OS was observed in secondary EMM patients with both del(1p32) and 1q21 gains, namely 2.7 months

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**Fig. 1 Chromosomal aberrations visualized in individual patient's paired samples.** BMPCs—bone marrow plasma cells. TPCs—plasmacytoma tissue plasma cells. HRD—hyperdiploidy. Numbers in boxes indicate the number of clones found for individual aberration.

**Table 1.** Cytogenetic data of patients' groups.

Category	NDMM without plasmacytoma (N = 243)	Primary EMM (N = 111)	Secondary EMM (N = 56)	p-value <sup>a</sup>
t (4;14)	9.1% (22/243)	9.9% (11/111)	14.3% (8/56)	0.499
t (14;16)	2.9% (7/243)	3.6% (4/111)	1.8% (1/56)	0.916
Del(13q14)/monosomy 13	54.7% (133/243)	56.8% (63/111)	69.6% (39/56)	0.124
Gain (1q21)	35.6% (84/243)	36.0% (40/111)	44.6% (25/56)	0.477
Amp (1q21)	12.3% (30/243)	12.6% (14/111)	16.1% (9/56)	0.477
Del (1p32)	11.1% (27/243)	20.7% (23/111)	28.6% (16/56)	<b>0.002</b>
Del (1p32) + 1q21	6.2% (15/243)	12.6% (14/111)	25.0% (14/56)	<b>&lt;0.001</b>
Chromosome 1 polysomy	6.6% (16/243)	7.2% (8/111)	3.6% (2/56)	0.640
Del (17p)/monosomy 17	13.6% (33/243)	18.9% (21/111)	32.1% (18/56)	<b>0.004</b>
Chromosome 17 polysomy	15.6% (38/243)	18.9% (21/111)	14.3% (8/56)	0.653

<sup>a</sup>Fisher exact test. Bold values indicate statistically significant results

(95% CI: 1.9–8.9), compared to 1.7 months (95% CI: 0.6–NA) and 22.2 months (95% CI: 10.6–NA), respectively ( $p < 0.001$ ).

Baseline clinical characteristics and survival data of primary and secondary EMM patients in the context of chromosome 1 aberrations are shown in Supplementary Tables 2, 3A, 3B and Supplementary Figs. 3 and 4.

In conclusion, we found chromosome 1 aberrations in nearly all our paired samples with a slightly higher incidence in plasmacytoma tissue rather than bone marrow compartment. Moreover, we encountered very high intra-patient heterogeneity in the 1q21 region between BMPCs and TPCs samples. Our findings were in accord with other studies investigating plasmacytoma tissue samples, reporting the comparable prevalence and variability of these aberrations, with respect to the different detection limits of FISH analyses [5–8]. According to these findings, 1q21 gains appear to be a rather later event or aberration undergoing significant evolutionary changes within cancer cell lines [9]. Our findings regarding del(17p) revealed a shared pattern between BMPCs and TPCs in less than half of the samples bearing this aberration. Similar to 1q21 gains, del(17p) may represent a later event in EMM development [6–8].

The strong negative prognostic impact of del(1p32) in MM patients has been repeatedly confirmed [10, 11], and it is more

pronounced in biallelic deletions or in combination with other high-risk aberrations, such as t(4;14), 1q21 gains or del(17p) [11]. Our results are consistent with these findings, highlighting the surprising association of this aberration with EMM patients. The highest incidence of del(1p32) along with 1q21 gains was observed in patients with secondary EMM, known for their poor prognosis [12]. The prognostic impact of these two aberrations combined was more severe across EMM patients than that of del(1p32) or 1q21 gains alone. Unfortunately, we were unable to detect biallelic deletions of 1p32 using I-FISH. These ultra-high-risk aberrations are rare, occurring in approximately 2% of cases. Other methods, such as single-nucleotide polymorphism arrays or next-generation sequencing, may be more effective in detecting them [11].

In the analysis of paired samples, deletions of 1p32 were found exclusively in secondary EMM patients, consistent with the population data mentioned above. Moreover, we observed this aberration more frequently in patients with EMD plasmacytomas. This coincidence may indicate a relation between del(1p32) and this aggressive entity [12]. The deletions of 1p32 were shared between bone marrow and plasmacytoma tissue in almost all cases. Shared deletions of 1p32 were also shown in the work of Liu Y et al. [7]. Compared to aberrations in the 1q21 region or TP53

deletions, our observation suggests that del(1p32) is likely a more conservative high-risk event in the clonal evolution and may play an important role in the initial stages of extrasosseous disease development. Based on our results, we strongly recommend including the detection of del(1p32) alongside 1q21 gains in the standard prognostic assessment for MM patients.

Martin Stork<sup>1,7</sup>✉, Eva Ondrouskova<sup>1,7</sup>, Michaela Bohunova<sup>1</sup>, Ivanna Boichuk<sup>1</sup>, Dominik Fric<sup>1</sup>, Zdenek Adam<sup>1</sup>, Marta Krejci<sup>1</sup>, Viera Sandecka<sup>1</sup>, Zdenka Knechtova<sup>1</sup>, Lenka Radova<sup>2,3</sup>, Zuzana Jelinkova<sup>4</sup>, Tatana Adlerova<sup>4</sup>, Milan Krticka<sup>5</sup>, Vladimir Nekuda<sup>5</sup>, Marek Borsky<sup>1</sup>, Sabina Sevcikova<sup>6</sup>, Marie Jarosova<sup>1,2,3</sup> and Ludek Pour<sup>1</sup>

<sup>1</sup>Department of Internal Medicine, Hematology and Oncology, University Hospital Brno and Faculty of Medicine, Masaryk University, Brno, Czech Republic. <sup>2</sup>Central European Institute of Technology, Masaryk University, Brno, Czech Republic. <sup>3</sup>Department of Medical Genetics and Genomics, Faculty of Medicine, Masaryk University and University Hospital Brno, Brno, Czech Republic. <sup>4</sup>Department of Burns and Plastic Surgery, University Hospital Brno and Faculty of Medicine, Masaryk University Brno, Brno, Czech Republic. <sup>5</sup>Trauma Surgery Department, University Hospital Brno and Faculty of Medicine, Masaryk University, Brno, Czech Republic. <sup>6</sup>Babak Myeloma Group, Department of Pathophysiology, Faculty of Medicine, Masaryk University, Brno, Czech Republic. <sup>7</sup>These authors contributed equally: Martin Stork, Eva Ondrouskova. ✉email: stork.martin@fnbrno.cz

## DATA AVAILABILITY

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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## AUTHOR CONTRIBUTIONS

SM, OE, and PL designed the study. OE and BohM performed the FISH analysis, JM analyzed and evaluated the FISH data. SM, OE, BI, FD, AZ, KM, SV, KM, BorM, SS, JM, and PL co-wrote the paper. JZ, AT, KM, NV selected patients for tissue sampling and provided surgical biopsies. KZ and RL analyzed data. All authors critically reviewed and approved the manuscript.

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## COMPETING INTERESTS

The authors declare no competing interests.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Ethics Committee of the University Hospital Brno, Czech Republic (2016). Informed consent was obtained from all subjects involved in the study.

## ADDITIONAL INFORMATION

**Supplementary information** The online version contains supplementary material available at <https://doi.org/10.1038/s41408-024-01131-6>.

**Correspondence** and requests for materials should be addressed to Martin Stork.

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