Atypical deletion of 5q in myelodysplastic syndromes (MDS) with retained commonly deleted regions (CDR) in MDS

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Introduction

The interstitial deletion of the long arm of chromosome 5 – del(5q) - is a recurrent cytogenetic aberration in bone marrow cells of patients with myelodysplastic syndromes (MDS). The extent of the del(5q) varies in individual cases, but chromosome region 5q31 is deleted in most of them.

Two different commonly deleted regions (CDRs) have been identified: the proximal 5q31.2 region is associated with a high-risk MDS, and the distal CDR 5q32–5q33 is involved in the pathogenesis of MDS with isolated del(5q) [1]. However, rare cases of atypical deletions of 5q that do not include defined CDRs have also been reported [2,3].

The aim of this study was to determine the frequency and clinical significance of atypical deletions of 5q in a large cohort of MDS patients.

Introduction

https://www.revlimid.com/mds-patient/about-myelodysplastic-syndromes/ what-is-myelodysplastic-syndromes/
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**Methods**

In the *1993-2019* we examined bone marrow cells of *3 714 MDS patients* with combination of cytogenomics techniques (retrospective and/or prospective analysis).

- **Conventional cytogenetic analysis (G-banding)** → karyotype at the time of diagnosis and during the disease
- **I-FISH** (Vysis DNA Probes, Abbott / XL Probes MetaSystems) → confirmation of del(5)(q31); monitoring the size of the pathological clone; verification of aberrations detected with conventional cytogenetic analysis
- **mFISH** (MetaSystems) → analysis of structural and/or complex chromosomal aberrations
- **mBAND** (MetaSystems) → analysis of the extent of del(5q); identification of breakpoints
- **aCGH/SNP** (CytoChip Cancer SNP 4x180K, Illumina / SurePrint G3 Cancer CGH+SNP Microarray, 4x180K, Agilent) → analysis of the size of del(5q) and other unbalanced aberrations
Results

Atypical deletion of 5q in myelodysplastic syndromes (MDS) with retained commonly deleted regions (CDR) in MDS

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Age</th>
<th>WHO 2016</th>
<th>HGB g/L</th>
<th>ANC x10⁹/L</th>
<th>PLT 10⁹/L</th>
<th>BM blasts (%)</th>
<th>IPSS-R score</th>
<th>IPSS-R category</th>
<th>Date of dg</th>
<th>Date of death</th>
<th>OS* months</th>
<th>Karyotype (G-banding, mFISH/mBAND)</th>
<th>FISH 5q31/q33</th>
<th>aCGH deletion size (Mb)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>66</td>
<td>MDS-EB 2</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>1993</td>
<td>1994</td>
<td>12</td>
<td>45,XX,t(2;11)(p16;q24),-del(5)(q12.1q23.3)[3]/46,XX[3] negative</td>
<td>71.9</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>61</td>
<td>AML-MRC</td>
<td>14.3</td>
<td>2.20</td>
<td>140</td>
<td>1.6</td>
<td>1</td>
<td>very low</td>
<td>1996</td>
<td>2019</td>
<td>271</td>
<td>46,XX,del(5)[q14.2q21.3][4]/46,XX[25] negative</td>
<td>27.7</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>59</td>
<td>MDS-SLD</td>
<td>8.3</td>
<td>2.76</td>
<td>172</td>
<td>0.4</td>
<td>2</td>
<td>low</td>
<td>2015</td>
<td>2015</td>
<td>6</td>
<td>46,XX,del(5)[q14.2q31.1][11]/46,XX[8] negative</td>
<td>53.19</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>83</td>
<td>sMDS-U</td>
<td>11.2</td>
<td>4.58</td>
<td>193</td>
<td>0.2</td>
<td>1</td>
<td>very low</td>
<td>2019</td>
<td>8</td>
<td>8</td>
<td>46,XY,del(5)[q14.3q22.2][20] negative</td>
<td>25.46</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>76</td>
<td>MDS-U</td>
<td>9.0</td>
<td>5.10</td>
<td>66</td>
<td>0.0</td>
<td>4.5</td>
<td>intermediate</td>
<td>2014</td>
<td>2015</td>
<td>9.5</td>
<td>46,XX,del(5)[q14.3q23.1],del(5)[q11.21q13.3][15] negative</td>
<td>30.75</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>66</td>
<td>MDS/MPN-U</td>
<td>12.2</td>
<td>11.00</td>
<td>50</td>
<td>2</td>
<td>1.5</td>
<td>very low</td>
<td>1999</td>
<td>2000</td>
<td>13.5</td>
<td>46,XX,del(5)[q14.3q23.2][20] negative</td>
<td>39.53</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>73</td>
<td>MDS-SLD</td>
<td>9.4</td>
<td>4.30</td>
<td>147</td>
<td>0.9</td>
<td>2</td>
<td>low</td>
<td>2010</td>
<td>2010</td>
<td>12</td>
<td>46,XY,del(5)[q14.3q23.2][19]/46,XY[3] negative</td>
<td>37.49</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>72</td>
<td>sMDS-U</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>2011</td>
<td>2011</td>
<td>11</td>
<td>46,XY,del(5)[q14.1q23.3][6]/46,XY[27] negative</td>
<td>53.7</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>77</td>
<td>AML-MRC</td>
<td>11.9</td>
<td>1.54</td>
<td>126</td>
<td>0.8</td>
<td>3</td>
<td>low</td>
<td>2017</td>
<td>2017</td>
<td>1</td>
<td>45,XY,del(5)[q14.3q31.1],dic(18;20)[p11.1;p11.1][18]/46,XY[2] negative</td>
<td>43.92</td>
<td></td>
</tr>
</tbody>
</table>

* calculated from the date of the first bone marrow examination

| na = data not available |

> del(5q) was detected in **920/3714** patients (**24.8%**). Most of them had large deletions spanning whole 5q31 region and both defined CDRs.

> **Atypical deletions with retained CDRs** were identified in **9/920** cases (**1%**; four males, five females; median age, 72 years).

> In six cases del(5q) was a sole abnormality, in three patients it was detected in combination with additional chromosomal aberrations.

> Of the nine patients, eight died (**median OS 11.5 months**) and one patient lives (8 months from diagnosis).
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Results

- **Patient No. 5**: 46,XX,del(5)(q14.3q23.1),r(18)(p11.21q22.3),del(20)(q11.21q13.3)
- **Patient No. 3**: del(5)(q14.2q31.1), r(18)(p11.21q22.3)
- **Patient No. 4**: del(5)(14.2q31.1)
- **Patient No. 9**: del(5)(14.3q22.2)

Images show the chromosomal abnormalities for each patient.
In all nine cases, deletions were localized proximally to the 5q31 region and both CDRs.

The size of the deleted segments ranged from 25.46 to 71.90 Mb (median 39.53 Mb) and the region 5q14.3 - q21.3 (26.79 Mb) was deleted in all nine patients.

Many candidate genes, whose haploinsufficiency could lead to malignant transformation, have been identified in this region (for example CCNH, CHD, MAN2A1, ARRDC3, ELL2, etc.).

Our results suggest that del(5q) may occur outside the defined CDRs.

Although these findings are extremely rare, they show that also genes located outside known CDRs highly probably contribute to the malignant progression of MDS.

The identification of these genes will lead to better understanding of the MDS pathogenesis and may contribute to identification of new therapeutic targets.