Leukaemia Section

Review

+X solely in ALL

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Abstract

Review on +X solely in acute lymphoblastic leukemia, with data on clinics.

KEYWORDS

X chromosome gain, acute lymphocytic leukemia, gene downregulation, Down syndrome.

Identity

Disease

Acute lymphoblastic leukemia (ALL), virtually all cases display a B-cell phenotype (except 1 T-cell ALL described by Heerema et al., 1998).

Clincis and pathology

Figure 1. Fluorescence in situ hybridization with centromeric CEP X/Y probe (Abbott Molecular, Vysis, US) showing 2 copies of chromosome X (green signal) on metaphase and interphase cells. Partial karyotype showing an extra copy of chromosome X (inset).
Epidemiology
34 patients (17 males and 17 females) aged 1 to 67 years (median 6 years); among them 17 patients were pediatric cases aged 1 to 16 years (median 4 years) (Privitera et al., 1992; Dastugue et al., 1992; Pui et al., 1993; Kempski et al., 1997; Heinonen et al., 1999; Silva et al., 2002; Chan et al., 2003; Kristensen et al., 2003; Russell et al., 2009; Lundin et al., 2014; Olsson et al., 2015; Liu et al., 2016). Up to half of these patients were Down syndrome (DS) cases (n=16) aged 1 to 13 years (Kalwinsky et al., 1990; Dastugue et al., 1992; Pui et al., 1993; Kempski et al., 1997; Heinonen et al., 1999; Mullighan et al., 2009; Russell et al., 2009; Lundin et al., 2014;). Adult patients were 20 to 59 years old (median 38 years) (from the known data) (Fuscaldo et al., 1981; Foa et al., 2003; Yamamoto et al., 2004; Chapiro et al., 2010; Eyre et al., 2012; Safavi et al., 2015; Yasuda et al., 2016) (Table 1).

<table>
<thead>
<tr>
<th>Sex/Age</th>
<th>Karyotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 F/59</td>
<td>47,XX,+X</td>
</tr>
<tr>
<td>2 M</td>
<td>48,XY,+X,+21c</td>
</tr>
<tr>
<td>3 F/4</td>
<td>48,XX,+X,+21c</td>
</tr>
<tr>
<td>4 M/7</td>
<td>47,XY,+X/47,idem,add(11)(p15)</td>
</tr>
<tr>
<td>5 M/2</td>
<td>48,XY,+X,+21c</td>
</tr>
<tr>
<td>6 F/4</td>
<td>48,XX,+X,+21c</td>
</tr>
<tr>
<td>7 M</td>
<td>46,XY,+X,inv(9)c at relapse</td>
</tr>
<tr>
<td>8 F/3</td>
<td>47,XX,+X,+21c</td>
</tr>
<tr>
<td>9 M</td>
<td>47,XY,+X</td>
</tr>
<tr>
<td>10 F/3</td>
<td>48,XX,+X,+21c</td>
</tr>
<tr>
<td>11 F/16</td>
<td>47,XX,+X/47,idem,[(17)(q10)/47,idem,dup(1)(q21q32)]</td>
</tr>
<tr>
<td>12 F/16</td>
<td>47,XX,+X</td>
</tr>
<tr>
<td>13 M/21</td>
<td>48,XY,del(1)(p22);t(1;19)(q23p13),+mar/47,XY,+X</td>
</tr>
<tr>
<td>14 F/6</td>
<td>47,XX,+X</td>
</tr>
</tbody>
</table>

Table 1. Clinical and karyotypic data of ALL patients with +X as a sole anomaly.

Abbreviations: M, male; F, female
**Prognosis**

+X as the sole anomaly may have not affect the prognosis in ALL patients and likely should be considered an indicator of low risk factor (Dastugue et al., 1992).

**Cytogenetics**

**Additional anomalies**

Out of 34 patients, the extra chromosome X was observed in a sideline in 5: in association with add(11)(p15) in 1 (Privitera et al., 1992), i(17)(q10) / dup(1)(q21q32) in 1 (Silva et al., 2002), del(1)(p22), t(1;19)(q23p13) in 1 (Foa et al., 2003), i(17)(q10) in 1 DS (Mullighan et al., 2009) and +17 in other DS patient (Russell et al., 2009).

**Result of the chromosomal anomaly**

**Fusion protein**

**Oncogenesis**

X-chromosome aneuploidy is a known numerical anomaly in ALL, especially in childhood ALL where it can be detected in nearly all children with a high hyperdiploid karyotype (Heinonen et al., 1999). It is also the most common acquired changes in DS-ALL were it is observed in between 25% and 50% of patients (Pui et al 1993). However, the acquired gain of an X chromosome as a sole abnormality has been observed only in a relatively small number of ALL patients. Notably, up to half of the cases were described in pediatric patients with Down syndrome, indicating that combination of trisomy 21 and +X chromosome seems to be typical of DS-ALL that and may lead to collaboration of genes on chromosomes 21 and X (Malinge et al., 2009). The result of chromosome X gain is an increased gene dosage that alters expression of many genes at the same time some of which could promote oncogenesis. In addition to an increased dosage of genes on chromosome X, recurring cryptic anomalies such as interstitial deletion of Xp22.33/Yp11.32 that juxtaposes the first, noncoding exon of P2RY8 (pseudautosomal region 1 of chromosomes X and Y) with the coding region of CRLF2 (cytokine receptor-like factor 2) or translocations t(X;14) between these regions and the immunoglobulin heavy chain locus at 14q32.33 may contribute to leukemogenesis in B-cell acute lymphoblastic leukemia (Mullighan 2009; Russell et al., 2009).

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