t(1;11)(p32;q23)

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Identity

Clinics and pathology

Disease
Acute lymphoblastic leukaemia (ALL), biphenotypic acute leukaemia (BAL), acute myeloid leukaemia (AML), and myelodysplastic syndrome (MDS).

Note
36 cases are available to date (Kaneko et al., 1986; Gregoire et al., 1987; Selypes and Laszlo, 1987; Hagemeijer et al., 1987; Hayashi et al., 1989; Raimondi et al., 1989; Shippey et al., 1989; Pui et al., 1990; Lampert et al., 1991; Abshire et al., 1992; Bernard et al., 1994; Felix et al., 1995; Felix et al., 1998; Harrison et al., 1998; Laughlin et al., 1998; Pinto et al., 1998; Secker-Walker et al., 1998; Nakamura et al., 2000; von Bergh et al., 2000; Chessells et al., 2002; Kim et al., 2002; Tsuijoka et al., 2003; Douet-Guilbert et al., 2005; Sagawa et al., 2006; Jeon and Yi, 2009; de Braekeleer et al., 2010; Shinohara et al., 2010); we have excluded from this review a case of t(1;6;11)(p32;q21;q23) in a T-cell lymphoma referred as "T-CLL", as it probably represents another entity (Mecucci et al., 1988). We must also keep in mind that some of the t(1;11)(p32;q23) above harvested may not all share the common genetic event 5' MLL - 3' EPS15: a case of t(1;11)(p32;q23), del(5q), +8 in a patient with therapy-related leukaemia has recently been described without MLL rearrangement (Yamamoto et al., 2010). There are also 3 paediatric cases (2 ALLs, 1 AML) of MLL/EPS15 translocation which were not included in this study, due to the lack of clinical data (Meyer et al., 2006).
Phenotype/cell stem origin
About half cases were ALLs and half cases AMLs. There were 17 ALLs, (mainly CD19+, CD10-) 2 biphenotypic leukaemias, 15 AMLs (of which were three M4-AMLs and nine M5-AMLs), and two MDS. There were at least nine cases of secondary leukaemia (and also 3 cases of "relapse", but each time with a different karyotype; e.g. a M1-AML with the classical t(8;21)(q22;q22) relapsed 16 months later with a t(1;11) as the sole anomaly (Hayashi et al., 1989)). The delay before onset of the secondary leukaemia - including the so-called relapses - was very similar, from a case to another, with a median of 16-21 months (range 12-24 months), if we exclude a case with an interval of 46 years after nuclear bombing (Nakamura et al., 2000). The previous disease was a haematological malignancy in seven cases (MDS, AML, ALL, multiple myeloma, non Hodgkin lymphoma (NHL)), a soft tissue tumour in three cases (primitive neuroectodermal tumour (PNET), PEComa, osteogenic sarcoma), and a breast cancer. The second leukaemia was an ALL in 6 cases, and a myeloid leukaemia (MDS or AML) in 6 cases.

Epidemiology
There was 12 male and 23 female patients (non significant: epsilon = 1.86, 0.07 < p < 0.06). However, while there was 8 male and 10 female patients in myeloid cases, there was only 3 male patients and 13 female patients with ALL (chi2 = 6.25 p < 0.02). Patients median age was 4 years (range 0-76 years); thirteen cases (38%) were infant cases (at or under 1 year of age), seven cases (20%) were between 1 and 10 years, three cases between 10 and 16, and twelve cases (1/3) were adult cases. Median age was 7 years in myeloid cases versus 1 year in lymphoid cases (ranges were 0.2-76 years and 0-63 years respectively, but with 5 cases and 1 case above 60 years respectively). About half of female cases (11/23), but only 2 of 11 male cases were congenital leukaemias (diagnosis at or before one year of age), although the ranges were similar, with cases above the sixties in both genders this is not statistically significant (chi2 = 2.77, 0.05 < p < 0.10). Median age in female patients was 2-3 years vs 7 years for male patients, ranges were similar.

Clinics
A high white blood count was noted in 9 of 11 documented cases.

Prognosis
Median survival was 15 months (see figure), with a very few long survivors (a patient was still alive 140 months after diagnosis (Chessells et al., 2002)). Median survival for female patients was 28 months, vs 11 months in male patients; Survival was significantly different according to the sex of the patients (chi2 = 4.66, p < 0.05, log rank test at 16 months). Survival curves for ALL and AML cases cross each other, with a median survival at 28 months for ALL cases and only 14 months for AML cases, but with no statistical significance. There was no correlation between age of the patient and survival. All the same and more surprisingly, the few patients with a secondary leukaemia with data on survival (n=6) did not seem to behave more badly than de novo cases. Also, the presence or the absence of chromosomal anomalies additional to the t(1;11) did not seem to affect the prognosis.

Cytogenetics
Cytogenetics morphological
The t(1;11) was the sole anomaly in 19 of 33 documented cases (57%), equally distributed between ALL and AML cases. There was two complex (three way) translocations: a t(1;11;4)(p32;q23q13;p16) and a t(1;11;10)(p32;q23;q24) (Selypes and Laszlo, 1987; de Braekeleer et al., 2010).

Additional anomalies
A trisomy 8 was found in four cases, a trisomy 21 in two cases, a del(5q) or a monosomy 7 in one case each.
Karyotypes were similar in ALL and myeloid cases, apart from that trisomy 8 was found as an accompanying anomaly in 3 myeloid and only one lymphoid cases, and that the cases with either del(5q) or -7 were found in myeloid cases. A complex karyotype was present in two myeloid cases.

**Genes involved and proteins**

**EPS15 (epidermal growth factor receptor pathway substrate 15)**

**Location**
1p32

**Protein**
A major transcript of 5225 bp produces a 896 amino acids protein from 25 exons; at least 5 other splice variants from 30 different exons. Contains from N-term to C-term: 2 EH (Eps15 Homology) domains (protein-protein interaction modules) with calcium-binding domains (EF hand domains), binding sites to adaptins, SH3 binding site, prolin-rich motifs, ubiquitin interacting motifs (UIM), and a nuclear export signal in C-term. There are also DPF repeats in the C-term third of the protein. Membrane receptor tyrosine kinase signaling inhibition is accomplished by ligand/receptor complexes internalization, subsequent trafficking to lysosomes and ubiquitination. EPS15 is involved in this process. EPS15 has a role in clathrin-mediated endocytosis, and may also have a role in transcriptional regulation (review in van Bergen and Henegouwen, 2009).

**MLL**

**Location**
11q23

**Protein**
A major transcript of 14982 bp produces a 3969 amino acids protein from 36 of the 37 exons. Contains from N-term to C-term a binding site for MEN1, 3 AT hooks (binds to the minor groove of DNA); 2 speckled nuclear localisation signals; 2 repression domains RD1 and RD2; RD1 or CXXC; cystein methyl transferase, binds CpG rich DNA, has a transcriptional repression activity; RD2 recruits histone desacetylases HDAC1 and HDAC2; 3 plant homeodomains (cystein rich zinc finger domains, with homodimerization properties), 1 bromodomain (may bind acetylated histones), and 1 plant homeodomain; these domains may be involved in protein-protein interaction; a FYRN and a FRYC domains; a transactivation domain which binds CBP; may acetylates H3 and H4 in the HOX area; a SET domain; a transactivation domain that binds TFIID. General transcription factor; maintains HOX genes expression in undifferentiated cells. Major regulator of hematopoiesis and embryonic development; role in cell cycle regulation.

**Result of the chromosomal anomaly**

**Hybrid gene**

**Description**
Variable breakpoint in MLL; fusion of exon 6 to 10 of MLL to exon 2 of EPS15 in most studied cases; in one case the fusion exon of EPS15 was exon 12, but it also retains the coiled-coil domain of EPS15; in other cases, the breakpoint is upstream exon 1.

**Fusion protein**

**Oncogenesis**
The coiled-coil domains of EPS15 mediates oligomerization, activating MLL, and MLL-EPS15 activates Hox gene expression (So et al., 2003).

**References**


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