del(5q) in acute lymphoblastic leukemia (ALL)

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Abstract

Myelodysplastic syndrome (MDS) with an isolated 5q deletion (5q-syndrome), that may arise de novo or may be therapy-related is recognized as a distinct entity by the WHO classification. While del(5q) thought to contribute to the pathogenesis of myeloid neoplasms, it has also been reported in lymphoblastic leukemia, suggesting a common underlying mechanism.

Keywords
Myelodysplastic syndrome; acute lymphoblastic leukemia; lenalidomide; 5q- syndrome; tumor suppressor genes.

Identity
See Figure 1.

Clinics and pathology

Disease
Acute lymphoblastic leukemia

Etiology
Acute leukemia evolving from an underlying MDS with del(5q) is almost always of myeloid lineage and only anecdotal case reports of MDS transforming to ALL have been reported (Agostino et al., 2011; Jain et al., 2016). Whether the presence of del(5q) in these cases reflects the underlying myelodysplastic state that later evolved into ALL remains unclear. del(5q) in ALL is mostly associated with multiple cytogenetic abnormalities that thought to be due to clonal expansion from an abnormal pluripotent stem cell.

Figure 1. (A). Fluorescence in situ hybridization with Vysis LSI CSF1R (5q33-34)/5p15.2 probe (Abott Molecular/Vysis, US) showing 2 red and 2 green signals on a normal metaphase and only 1 red signal on a metaphase with 5q deletion. Inset: Partial karyotype with 5q deletion and with chromosome 5 in 'action' (chromosome 5 breaks).
Epidemiology
At least 160 reported patients aged 0 to 86 years (98 males, 61 females, 1 unknown); prevalence of pediatric patients (86 patients) and there were 46 adults.

B-cell acute lymphoblastic leukemia: 70 patients aged 0 to 86 years (41 males and 28 females, 1 unknown); among them there were 22 adults (14 males and 8 females, aged 22 to 86 years; median 42 years) and 39 pediatric patients (22 males and 17 females, aged 0 to 18; median 6 years). In addition, there were 9 patients with unknown age (5 males and 3 females, 1 unknown).

T-cell acute lymphoblastic leukemia: 58 patients (35 males and 23 females aged 1 to 79 years); among them there were 17 adults (9 males and 8 females aged 19 to 79 years), 35 pediatric patients (22 males 13 females aged 1 to 18 years) and 6 patients with unknown age (4 males and 2 females).

32 patients had unspecified ALL (22 males, 10 females aged 3 to 81 years; median 13 years); 7 patients were adults (5 males and 2 females) aged 34 to 81 years (median 72 years), 12 were pediatric patients (8 males and 4 females aged 3 to 16 years; median 6 years) and there were 12 patients with unknown age (8 males and 4 females).

Clinics
In contrast to its presence in myeloid malignancies, isolated del(5q) is rare in ALL, thus its clinical significance is unknown. del(5q) also appears to be clinically insignificant in patients following cytotoxic therapy or tyrosine kinase inhibitor (TKI) therapy, similar to other clonal cytogenetic abnormalities if detected as a minor clone (Tang et al., 2015). del(5q) in ALL mainly found as a clonal evolution event associated with disease progression.

Genetics
Del(5q) may be found as sole abnormality at first, as an evolutionary event in other cases, and as a transient event in patients after being treated with cytotoxic agents or TKI for the prior malignancies.

Cytogenetics

Cytogenetics morphological
Excluded are patients with EBF1/PDGFRB fusion that arose from interstitial deletion of 5q33, occurring within the Philadelphia-like ALL subtype. Del(5q) as a sole clonal cytogenetic abnormality was found in 11 patients (3 with B-ALL, 4 with T-ALL and 4 with unspecified ALL) (Kowalczyk et al., 1985; Brusamolino et al., 1988; Raimondi et al., 1988; Loncarevic et al., 1999; Midmer et al., 1999; Gmidene et al., 2008; Palau et al., 1991; Valtat et al., 1991; Theodossiou et al., 1992; Goud et al., 2015).

Among these patients, there was and a 5-year-old boy who had previously received chemotherapy for ALL that had been diagnosed nine months before (Palau et al., 1991), a 13-year-old boy in whom the rearrangement was transiently present 7 months following the diagnosis of Ph-positive ALL (Theodossiou et al., 1992).

Del(5q) with other abnormalities Found in a sideline with del(20q) and +Y in 2 MDS patients transforming to B-ALL while on lenalidomide (Agostino et al., 2011) and with limited additional anomalies such as i(7)(q10) in 1 (Kaneko et al., 1989), +22 in 1 (Karst et al., 2006), der(19)t(1;19)(q23;p13) in 1 (Chen et al., 1992) and 1 had a clone with a Ph chromosome and del(5q) at diagnosis (Takechi et al., 1990). The t(12;21)(p13;q22) was present as a sole additional anomaly in 3 patients with B-cell ALL (Lu et al., 2002; South et al., 2006; Zhou et al., 2012) and in 8 it was part of a complex karyotype (Alvarez et al., 2005; Kuchinskaya et al., 2005; Jarosova et al., 2003; Martineau et al., 2005; Olsson et al., 2018), however it is possible that some additional pediatric patients had a cryptic t(12;21). 3 patients had dic(9;20) (Heerema et al., 1996; Strefford et al., 2007; An et al., 2008), 10 t(9;22) (q34;q11) (Sessarego et al., 1991; Tsuchiya et al., 1995; Rieder et al., 1996; Lee et al., 2002; Onciu et al., 2002; Wetzler et al., 2004; Russell et al., 2008; De Braekeleer et al., 2010; Lundin et al., 2014; Olsson et al., 2018) in complex karyotypes. The majority of patients with T-ALL had karyotypes with combination of chromosome deletions and specific translocations such as t(4;11)(q21;p15) (Hussey et al., 1999), t(5;14)/HOX11L2 (Berger et al., 2003; Bernard et al., 2001), t(4;11)(q23;p15) (Zhang et al., 2012), t(7;10)(q34;q22) (Lai et al., 2000), t(7;11)(q35;p13) (Kaneko et al. ID: >1998), t(10;11)(p12;q21) (Matlawsk-Wasowska et al., 2016), t(10;14)(q24;q11) (Grossmann et al., 2013) and inv(7)(p15q34) (Rowley et al., 1999; La Starza et al., 2016).

Genes involved and proteins
Deletions of 5q are heterozygous, and deleted regions can affect different genes that are involved in the regulation of hematopoiesis.

Result of the chromosomal anomaly
Fusion protein
Oncogenesis
Interstitial or terminal deletions of the long arm of
chromosome 5 are common findings in MDS or acute myeloid leukemia (AML), but they may also occur in patients with ALL. Deletions of genetic material from 5q result in loss of tumor suppressor genes that may potentially play a role in the pathogenesis of these diseases. The long arm of chromosome 5 contains many genes that are relevant in hematopoiesis and several candidate genes including transcription factors, cytokines and their receptors, signal mediators and cell cycle regulators have been identified. These include the RPS14 gene on 5q33.1, a critical gene for the erythroid phenotype, a microRNA cluster on 5q32-33 important for the megakaryocytic phenotype, the EGR1 gene on 5q31 that plays a role in hematopoietic stem cell proliferation. Other genes such as NPM1 and APC, the transcription factor Egr1/Krox20, the cytoskeletal remodeling protein, alpha-catenin may also contribute to the disease phenotype and progression (Tang et al., 2015). Although a critical tumor suppressor gene has not yet been identified in ALL, several putative tumor suppressors such as NR3C1 and TCF7, located within the 5q31 common deleted region and TRIM41, ZFP62, MAPK9, MGAT1, and CNOT6, mapping at 5q35 have been found to be down-regulated in T- ALL (La Starza et al., 2016). Given the large size and variable pattern of 5q deletions, it is probable that the loss of several genes that act alone or in combination contribute to pathogenesis. The absence of a clear critical gene suggests that deletion of variable combinations of genes may result in a clinical spectrum ranging from myeloid malignancies to lymphoid leukemia.

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