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Leukaemia Section
Short Communication

Early T-cell precursor acute lymphoblastic leukemia

Steven Richebourg

Laboratoire de cytogénétique onco-hématologique, Département de pathologie, Hôpital du Saint Sacrement, CHU de Québec Université Laval, 1050, Chemin Sainte Foy, Département de Médecine Moléculaire, Faculté de médecine, Université Laval, Québec, G1S4L8 Québec, Qc, Canada; steven.richebourg.cha@ssss.gouv.qc.ca

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Abstract

Review on early T-cell precursor acute lymphoblastic leukemia, with data on clinics and the genes possibly involved.

Keywords
T-cell; acute lymphoblastic leukemia

Identity

Other names
Early T-cell precursor lymphoblastic leukemia/ETP-ALL/ETP T-ALL

Clinics and pathology

Note
Identified in 2009 from gene expression profiling data, Early T cell Precursor Acute Lymphoblastic Leukemia (ETP-ALL) represents a subset of T-ALL sharing transcriptional and immunophenotypic similarities with early T-cell precursors (Coustan-Smith et al., 2009).
ETP-ALL is currently defined by a distinctive phenotype characterized by a lack of expression of the T-lineage cell surface markers CD1a and CD8, weak or absent expression of CD5 and aberrant expression of one or more myeloid or stem cell markers (Coustan-Smith et al., 2009).
Since the description, genetic alterations and prognostic data have been reported in literature improving our understanding of this subgroup. Therefore, ETP-ALL has been included as a provisional entity in the 2016 revision of the WHO classification of Acute Leukemias (Arber et al., 2016).

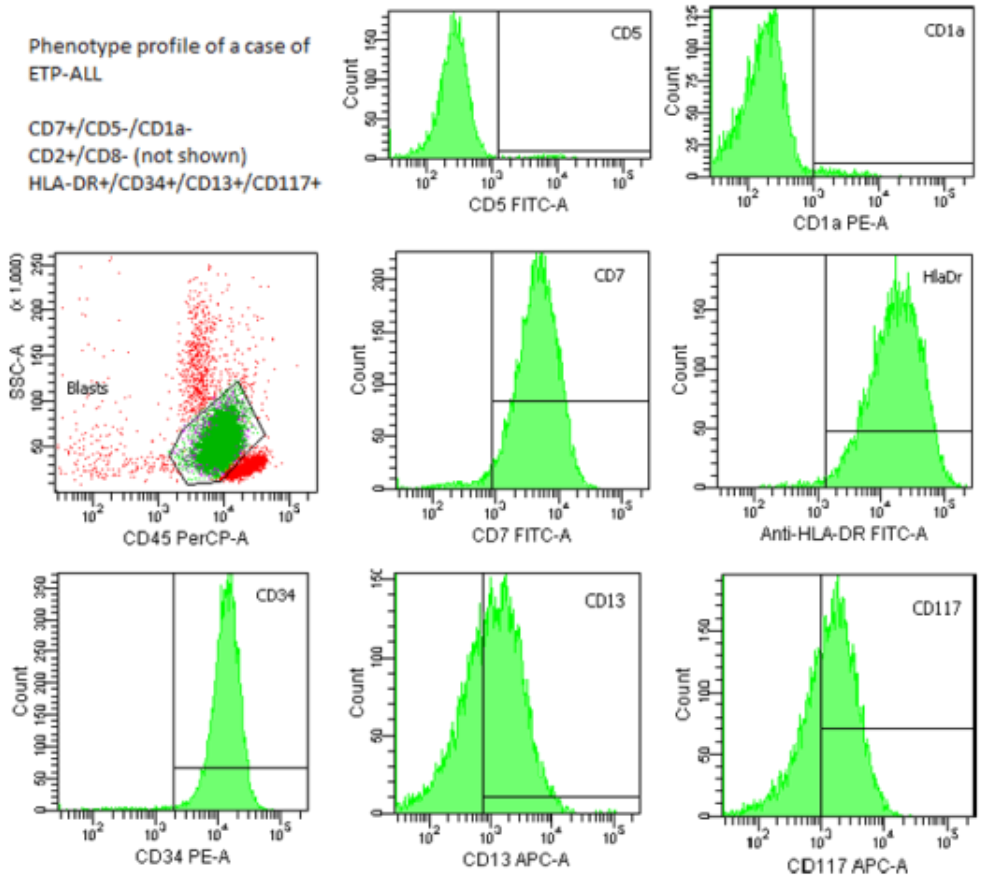
Disease

Phenotype/cell stem origin

Early T-cell precursors (ETPs) are immature progenitors that have recently immigrated from the bone marrow to the thymus and which retain a multilineage differentiation potential (T-lymphoid, natural killer, dendritic and myeloid cell differentiation potential). Animal model based studies of ETPs demonstrate similarities with immature myeloid progenitors and hematopoietic stem cells (Bell and Bandhoola, 2008; Wada et al., 2008). Because gene expression profiling is not part of routine laboratory investigations, ETP-ALL cases are currently identified through the phenotype of blast cells : $CD1a^-$, $CD8^-$, $CD5^-$ /weak, and positivity for one or more stem cell and/or myeloid antigens (CD117, CD34, HLA-DR, CD13, CD33, CD11b, and/or CD65) (Coustan-Smith et al., 2009; Chopra et al., 2014). ETP-ALL typically also express CD2, CD7 and cytoplasmic CD3 and may express CD4.

Epidemiology

Initially described from children ALL cohorts, ETP-ALL have also been identified in adults. Frequency of ETP-ALL varies among studies around 10-15% of T ALL.



Courtesy Linda Boulay and Frédéric Barabé, Flow Cytometry Laboratory, Hôpital du Saint Sacrement, CHU de Québec Université Laval

In children, ETP-ALL has been reported in 11% to 16% of T-ALL (Coustan-Smith et al., 2009; Patrick et al., 2014).
In adults, ETP-ALL frequency ranges from 7,4% (Neumann et al., 2012) to 17% of T-ALL (Jain et al., 2016).
Based on gene expression profiling, some authors suggest that there is an immature signature related to ETPs (called "near ETP' or "close to ETP") which may be more prevalent (Van Vlierberghe et al., 2013; Haydu and Ferrando, 2013).

Clinics

Most studies report no significant association between ETP-ALL signature and clinical features including sex, age, white blood cell count, and central nervous system involvement (Coustan-Smith et al., 2009; Inukai et al., 2012; Neumann et al., 2012).
Though, two no recurrent features were identified : an older age in paediatric population (Coustan-Smith et al., 2009) and a lower frequency of mediastinal mass at diagnosis in adult population (Neumann et al., 2012).

Cytology

No specific morphologic features have been reported to date.

Treatment

Since there is no consensus on the prognosis (see below), no specific protocol is recommended. Because of the trend to negative impact on prognosis, some authors suggest that new therapeutic strategies are needed to improve the outcomes of ETP-ALL (Jain et al., 2016; Neumann et al., 2013), including the use myeloid-targeted therapies such as tyrosine kinase inhibitors (Neumann et al., 2012; Neumann et al., 2013; Zhang et al., 2012)

Prognosis

There is currently no consensus on the prognosis of ETP-ALL.
Initial prognostic studies between 2009 and 2012 reported a negative prognostic impact on response rate and survival (Coustan-Smith et al., 2009, Inukai et al., 2012; Ma et al., 2012) and a higher risk of relapse (Allen and al., 2013).
These data were not confirmed in more recent studies with larger cohorts (Brent et al., 2014; Patrick et al., 2014; Zuurbier et al., 2014).
However, in 2016, a MD Anderson study reported again a negative prognostic impact on the response rate and the overall survival of patients with ETP-ALL (Jain et al., 2016).

Cytogenetics

No specific cytogenetic abnormality is associated with ETP-ALL subtype.
In most studies, ETP-ALL patients present highly variable karyotypes with remarkably a lower frequency of classic recurrent rearrangements associated with T-ALL (Patrick et al., 2014).
Coustan Smith and al reported a higher frequency of deletion 13q (Coustan-Smith et al., 2009) and Patrick et al a higher frequency of KMT2A rearrangements (Patrick et al., 2014).
SNP analysis demonstrated a higher frequency of copy number alterations in ETP-ALL vs non ETP-ALL (Coustan-Smith et al., 2009).

Genes involved and proteins

ETP-ALL subgroup is characterized by a high genetic heterogeneity and present a distinct genomic profile defined by a lower incidence of typical mutations associated with T ALL such as NOTCH1 or FBXW7 and a high frequency of myeloid associated gene mutations (FLT3, RAS mutations, DNMT3A, IDH1 / IDH2 mutations) (Neumann et al., 2013; Van Vlierberghe et al., 2011; Zhang et al., 2012).
Whole exome and whole genome sequencing approaches identified mutations in multiple pathways including mutations in genes activating cytokine receptor and RAS signalling (NRAS , KRAS, FLT3, IL7R, JAK3, JAK1, SH2B3 and BRAF), inactivating haematopoietic transcription factors (GATA3, ETV6, RUNX1, IKZF1 and EP300) and in epigenetic regulators (EZH2, EED, SUZ12, SETD2 and EP300) (Zhang et al., 2012)

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