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Leukaemia Section
Review

Infant leukaemias, Congenital leukaemias, Neonatal leukaemias

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Abstract

Review on congenital/neonatal and infant leukemias, with data on clinics, pathology, and involved genes.

Keywords
congenital, infant, KMT2A, leukemia, neonatal

Identity

Congenital and neonatal leukemias are defined as those diagnosed within the first 4 weeks of life.
Account for <1% of childhood leukemias.
Infant leukemias are defined as those diagnosed within the first year of like.

Clinics and pathology

EPIDEMIOLOGY
Neonatal/congenital leukemia is estimated at 1-5 cases/million live births (~2 cases per year in the UK) (Roberts et al., 2018).
Infant leukemia is estimated at ~160 cases/year (41 cases per million) in the United States (Brown et al, 2019).
Infant ALL accounts for 2-5% of pediatric ALL cases (Pui et al., 1994).
Infant AML accounts for 6-20% of pediatric AML.
Data has shown that patients, diagnosed to have a leukaemia at age 5 mths and 2 yrs, already had a KMT2A/AFF1 (then MLL-AF4) fusion gene in their neonatal blood spots/Guthrie cards (Gale et al., 1997).

Infant leukaemias have been suspected to have an environmental component (Greaves, 1996):
- Some of the leukaemias known to be often related to genotoxic exposure, such as the 11q23 leukaemias and the t(8;16) leukaemia, may also be found in infants.
- There has been a significant increase in infant acute leukaemias incidence of around 2.5% per year for 15 yrs, suggesting the presence of an environmental factor.
- Studies have found an increased risk after maternal marijuana use and alcohol consumption.
- Maternal exposure to dietary flavonoids during pregnancy may contribute to the risk of KMT2A rearranged leukemias.
- Infants with leukaemia (excluding Down syndrome cases) have more congenital anomalies (heart defects, digestive tract anomalies, mental delay).

CLINICS
Sex ratio is balanced, both in AML and in ALL cases.

Neonatal leukemias:
Common to have hepatosplenomegaly (~80% of cases), skin lesions (leukemia cutis, ~50% of cases), CNS involvement (~50% of cases), and/or hyperleukocytosis.
Cutaneous involvement can be the presenting feature and can manifest as the so-called "blueberry muffin baby" appearance with blue, purple, brown, or red nodules.
- 2/3 of AML cases have cutaneous involvement.
- 1/2 of ALL cases have cutaneous involvement.

Anemia, thrombocytopenia, and neutropenia can lead to increased bleeding tendency, infections, and failure to thrive.

Infiltration of the CNS can cause cranial nerve palsies, seizures, and papilledema.

Meningeal infiltration can manifest as a bulging fontanelle.

Infant leukemias:

Many have aggressive features including high WBC counts, hepatosplenomegaly, frequent CNS involvement, and/or skin infiltrations (leukemia cutis).

PATHOLOGY/CYTOGENETICS

Neonatal leukemia - 2/3 AML; 1/3 ALL

Infant leukemia - more likely ALL than AML

ALL

11q23 (KMT2A) gene rearrangements in 70-80% of infants and up to 91% of those infants younger than 6 months (Pieters et al., 2007; Zweidler-McKay and Hilden, 2008).

Most common KMT2A partners are AFF1, MLLT1, MLLT3, and MLLT10 (Pieters et al., 2007).

Usually express CD19, CD22, and TdT by flow cytometry. Those without KMT2A fusions usually express CD10; those with KMT2A rearrangements often lack CD10 but express CD15.

AML

Usually myelomonocytic (FAB M4), monoblastic/monocytic (FAB M5), or megakaryoblastic leukemia (FAB M7).

11q23 (KMT2A) gene rearrangements in 50% of infants (Brown et al., 2019; Zweidler-McKay and Hilden, 2008).

Most common KMT2A partners are MLLT3, MLLT10, and ELL (Pieters et al., 2007)

Usually express CD13 and CD33 by flow cytometry; M4 and M5 also express CD14 and CD15; M7 also expresses CD61, CD42b, and/or CD41 by flow cytometry.

TREATMENT

ALL Interfant-99 protocol uses a 7-day prednisone prophase and then a hybrid regimen of standard ALL therapy with some AML therapy elements (including cytarabine) (Brown et al., 2019; Pieters et al., 2007).

AML Generally treated on the same clinical protocols as older children with multiagent chemotherapy plus CNS-directed therapy (Brown et al., 2019).

PROGNOSIS

ALL

4yr event free survival is 47% and 4-year overall survival is 55.3% (Pieters et al., 2007).

- However, 4-year EFS of those with KMT2A rearrangements was 37% compared to 74% in those without KMT2A rearrangements.

High WBC (>300 K/uL), young age (<6 months), presence of KMT2A rearrangement, and poor prednisone response were significant predictors of poor outcome (Pieters et al., 2007).

Survival after relapse is low, with 3-year overall survival after relapse of 20.9% (Driessen et al., 2016).

In those who relapse, outcome is negatively impacted by age at original diagnosis (<6 months of age), higher WBC count at diagnosis, and relapse within 1 year after diagnosis (Driessen et al., 2016).

In those with congenital leukemia, the 2-year EFS and OS is 20% (van der Linden et al., 2009).

AML

Outcomes are similar in infants to those of older children with 5-year overall survival of 51% and 5-year event free survival of 44%.

Spontaneous regression/remission can occur in rare cases (Bresters et al., 2002; Roberts et al., 2018; van den Berg et al., 2004).

Survivors of infant leukemia demonstrate increased risk of late effects including growth problems, learning difficulties, hypothyroidism, and pubertal development (Roberts et al., 2018).

Use of hematopoietic stem cell transplantation is controversial and findings are not conclusive as to whether it improves survival.

Disease

Transient abnormal myelopoiesis (TAM) of Down syndrome

Epidemiology

Restricted to newborns with trisomy 21 or mosaic for trisomy 21.

Clinics

Some infants (10-25%) are asymptomatic, only presenting with increased circulating blasts (Massey et al., 2006; Klusmann et al., 2008). Most neonates present at 3-7 days of age with a leukocytosis and an abnormal platelet count (usually thrombocytopenia, but thrombocytosis has also been identified). Hepatomegaly is common due to fibrosis and/or megakaryoblast infiltration. Other clinical findings include splenomegaly, exudative effusions (including pleural, pericardial, and ascites), and respiratory distress (due to hepatomegaly). In utero presentations include hydrops fetalis and anemia.

Genes

GATA1 somatic mutations are present.

Evolution

Spontaneous resolution of blasts and symptoms occurs in 66-84% of infants over a time period of 2-3 months without a need for intervention (Klusmann et al., 2008; Gamis et al., 2011). The remaining infants may need supportive therapy or chemotherapy. Overall, approximately 15-20% of cases still die, though some of these are due to other abnormalities associated with trisomy 21 (Klusmann et al., 2008; Gamis et al., 2011). Approximately 16-30% of infants, whether they were asymptomatic or had clinical symptoms, develop myeloid leukemia

associated with Down syndrome (Klusmann et al., 2008).

Disease

11q23 abnormalities

Phenotype/cell stem origin

Acute monoblastic/monocytic or myelomonocytic leukaemia (AML) or CD19+ B-cell acute lymphoblastic leukaemia (B-ALL).

Epidemiology

11q23 (KMT2A) gene rearrangements are in present in 70-80% of infants with B-ALL and up to 91% of those infants younger than 6 months with B-ALL (Pieters et al., 2007).
11q23 (KMT2A) gene rearrangements are present in 50% of infants with AML (Brown et al., 2019).

Clinics

Organomegaly; frequent CNS involvement; high WBC count (Huret et al., 1993; Johansson et al., 1998).

Pathology

In those with ALL and KMT2A gene rearrangements, flow cytometry immunophenotyping often shows expression of CD19, CD22, TdT, and CD15 with absence of CD10; CD13 an CD33 may be expressed.
In those with ALL and KMT2A gene rearrangements, there is often overexpression of FLT3.
In those with AML, there is often expression of CD13, CD14, CD15, and CD33.

Prognosis

4 year event free survival is 37% (Pieters et al., 2007).
t(4;11)(q21;q23) KMT2A/AFF1: may have worse outcome (Heerema et al., 1994)

Cytogenetics

t(4;11)(q21;q23) KMT2A/AFF1 : most common infant translocation; usually ALL (49% of B-ALL cases, and more often in those <6 months of age), but can be AML (<5%) (acute monoblastic/monocytic or myelomonocytic leukemia), or mixed phenotype acute leukemia (Johansson, et al., 1998).

t(9;11)(p23;q23) KMT2A/MLLT3 : found in 22% infant acute monoblastic/monocytic or myelomonocytic AML and 17% of infant ALL (Köller et al., 1989; Swansbury et al., 1998).
t(10;11)(p12;q23) KMT2A/MLLT10 : found in 27% infant acute monoblastic/monocytic or myelomonocytic AML and 5% of infant ALL (Lillington et al., 1998).
t(11;19)(q23;p13.3) KMT2A/MLLT1: found in 22% infant ALL, mixed phenotype acute leukemia, and 15% acute monoblastic/monocytic or myelomonocytic leukemia (Huret et al., 1993; Moorman et al., 1998).
t(11;19)(q23;p13.1) KMT2A-ELL: found in 17% AML, usually acute myelomonocytic or monoblastic/monocytic leukemia (Moorman et al., 1998).
other 11q23 rearrangements are rarely found in infants leukemias.

Disease

t(1;22)(p13;q13) RBM15/MKL1

Phenotype/cell stem origin

Acute megakaryoblastic leukemia (M7 AML).

Note

This is a cryptic fusion not identified by routine karyotyping, and usually requiring RNA sequencing for identification.

Epidemiology

This leukaemia is (nearly) restricted to infant cases; median age is 2-4 months (Bernstein et al., 1999; Chan et al., 1991; Lion and Haas, 1993); accounts for <1% AML.

Clinics

Organomegaly, liver and bone marrow fibrosis.

Prognosis

Remission is obtained in only half cases, median survival is 8 months (Bernstein et al., 1999).

Disease

AMkL with inv(16)(p13q24) CBFA2T3/GLIS2

Phenotype/cell stem origin

Acute megakaryoblastic leukemia in most cases, though rare other AML subtypes are identified with this fusion.

Epidemiology

Usually presents in infants (Bolouri et al., 2017; Hara et al., 2017).

Prognosis

Poor prognosis with 4-5-year OS ranging from 14-41.7% and 4-5-year EFS ranging from 8-33% (de Rooij et al., 2016; de Rooij et al., 2017; Hara et al., 2017).

Disease

AML with t(11;12)(p15;p13) NUP98/KDM5A

Phenotype/cell stem origin

Acute megakaryoblastic leukemia in most cases, though rare other AML subtypes are identified with this fusion.

Epidemiology

Can present in infants (de Rooij et al., 2016).

Prognosis

Usually a poor prognosis with 4-5-year OS ranging from 22-50% and 4-5-year EFS ranging from 22-36% (de Rooij et al., 2013; de Rooij et al., 2016; de Rooij et al., 2017; Hara et al., 2017).

Disease

inv(16)(p13q22)

Phenotype/cell stem origin

Myelomonocytic leukemia (M4 AML)

Epidemiology

At least 3 cases reported.

Clinics

High WBC, CNS involvement in 2/3 (Pui et al., 1987).

Disease

t(5;15)(p15;q11)

Phenotype/cell stem origin

B lineage ALL

Epidemiology

5 known cases (Heerema et al., 1994).

Prognosis

unknown; CR in 5/5.

Disease

t(8;16)(p11;p13) KAT6A/CREBBP

Phenotype/cell stem origin

Acute myelomonocytic or monoblastic/monocytic AML.

Clinics

Leukemia cutis, hepatosplenomegaly.

Prognosis

Has shown spontaneous regression in some cases, though some do relapse (Dinulos et al., 1997; Roberts et al., 2018) Other cases require chemotherapy from diagnosis.

Disease

Juvenile myelomonocytic leukemia

Epidemiology

Annual incidence is approximately 0.67 cases/million with a median age of 1.1-1.8 years and male to female ratio of 2-3:1. (Hasle et al., 1999; Niemeyer et al., 1997; Passmore et al., 2003).

Clinics

Splenomegaly, lymphadenopathy, and skin rashes are common (Hess et al., 1996).

The diagnostic criteria for JMML are (Locatelli and Neimeyer, 2015; Baumann, et al., 2017).

Clinical and hematologic features (all 4 required)

Peripheral blood monocyte count $\geq 1 \times 10^9$/L.

Peripheral blood and bone marrow blast percentages <20%.

Splenomegaly.

No Philadelphia (Ph) chromosome or BCR/ABL1 fusion.

Genetic criteria (1 finding is sufficient)

Somatic mutation in PTPN11, KRAS, or NRAS.

Clinical diagnosis of neurofibromastosis type 1 or NF1 mutation.

Germline CBL mutation and loss of heterozygosity of CBL.

Other criteria (those not meeting genetic criteria but having clinical and hematologic criteria must also have).

Monosomy 7 or any other chromosomal abnormality.

or ≥ 2 of the following:

Increased hemoglobin F (HbF) for age.

Myeloid or erythroid precursors on peripheral blood smear.

Granulocyte-macrophages colony-stimulating factor (GM-CSF) hypersensitivity in colony assay.

Hyperphosphorylation of STAT5.

Prognosis

Those with germline mutations in PTPN11, KRAS, NRAS, or CBL have disease that may spontaneously regress without therapy (Locatelli and Neimeyer, 2015).

However, in other cases HSCT is recommended, after which the 5-year overall survival rate is 64%, with an event free survival of 52% (Locatelli et al., 2005).

Genes involved and proteins

KMT2A (MLL)

Location

11q23

DNA/RNA

Encodes a histone-lysine N-methyltransferase, a 431 kDa protein; contains 3 AT hook DNA-binding domains, Zinc fingers, a SET domain which is responsible for its DNA methyltransferase activity, and a bromodomain.

Protein

Regulates gene expression during early development and hematopoiesis; regulates transcription of many target genes, including HOX genes.

The fusion proteins usually include the N-terminus AT hook and DNA methyltransferase from KMT2A fused to (little or most of) the partner C-term part from the other chromosome.

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