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Leukaemia Section

Mini Review

Infant leukaemias, Congenital leukaemias, Neonatal leukaemias

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Identity

Note: Infant or congenital leukaemias are defined by a diagnosis within either the first month, the first year, or the first two years of life, according to different workers; recent data have shown that patients, diagnosed to have a leukaemia at age 5 mths and 2 years, already had a MLL-AF4 fusion gene in their neonatal blood spots/Guthrie cards.

Infant leukaemias have been suspected to have an environmental component:

1- 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;

2- there has been a significant increase in infant acute leukaemias incidence of around 2.5% per year for 15 years, suggesting the presence of an environmental factor;

3- infants with leukaemia (excluding Down syndrome cases) have more congenital anomalies (heart defects, digestive tract anomalies, mental delay).

They may be myelodysplasia or acute non lymphocytic leukaemia (M4 or M5 mainly) in 1/2 to 2/3 of cases, or B-cell acute lymphocytic leukaemia (CD19+ or CD10+) in the remaining cases.

Sex ratio is balanced, both in ANLL and in ALL cases.

Frequent CNS involvement; WBC is often high, whatever the chromosome anomaly is; skin infiltrations (leukaemia cutis) may occur.

11q23 is found involved in 1/3 to 1/2 of cases (t(4;11), t(9;11), and t(11;19) representing nearly 1/10 of cases each).

See also 11q23 rearrangements in childhood acute lymphoblastic leukemia: Clinical aspects.

4 year event free survival in infants ALL is 1/3 and median event free survival (EFS) is 1 year.

In infants aged less than a month, 6 months survival is only 1/3, both in ANLL and in ALL.

As the prognosis is most often very poor, bone marrow transplantation is indicated, apart in infant leukemia of the Down syndrome patient, were the prognosis is good.

Clinics and pathology

Disease

Infant myelodysplasia.

Note

They most often exhibit a normal karyotype or a monosomy 7.

Etiology

Exhibit a genetic background or is considered as idiopathic.

Epidemiology

Annual incidence: about 1 case per 106.

Prognosis

Has herein been calculated from 3 large studies (n=47): median survival was 31 mths; 6 year survival was 43%.

Disease

Down syndrome with M7.

Note

Down syndrome patients have been known for long to be at increased risk (10 to 30 fold) of both ALL and ANLL; ALL is similar in Down syndrome (DS) and in the general population, whereas ANLL in DS is most often a specific entity of acute megakaryoblastic leukaemia (M7-ANLL); at least 20% of leukaemias in DS are M7, and other cases of M7-ANLL may also be misclassified as undifferentiated leukaemias or as ALL;

therefore, the risk of M7 may well be 500 to 1000 times greater when the child has a DS; in other words, it may be that half of infants with M7 are DS ... and also that the risk of ALL in DS may not be as increased as previously claimed.

Epidemiology

M7 leukaemia in Down syndrome infants annual incidence: 0.2 case per 106; median age at diagnosis is 22-23 mths.

Clinics

There is often a preceeding myelodysplasia, or history of transient leukemoid reaction (a disease of the megakaryocytic lineage).

Prognosis

M7-ANLL has proved to be of better prognosis when in DS, with a recent study on 65 DS patients with M7, showing a 4 yr event free survival of 73%.

Disease

11q23 abnormalities.

Phenotype/cell stem origin

M4 or M5 acute non lymphocytic leukaemia (ANLL) or CD19+ B-cell acute lymphocytic leukaemia (ALL).

Epidemiology

25% of 11q23 rearrangements cases are infant (<1 year) cases; as much as 2/3 of cases of infant ALL leukaemias have been found in some studies to carry a 11q23 rearrangement, especially in infants <6 mths old; a third to a half of infant ANLL cases also have a 11q23 rearrangement; however, 11q23 leukaemias can also be seen in children and in adults.

Clinics

Organomegaly; frequent CNS involvement; high WBC.

Prognosis

Median survival of 1 year, and a 3 year event free survival of 13% in a study and a 4 year event free survival of 15% in another.

- t(4;11)(q21;q23): CD19+ B-ALL; unbalanced sex ratio <4 yrs (1M/2F); infants (<1 year) accounting for 1/3 of t(4;11) cases; annual incidence could be 0.3-0.5 case per 106; prognosis: med EFS 7 mths; med survival 29 mths; 3 year survival 40%; 3 year EFS: 30%; the gene involved in 4q21 is AF4.
- t(9;11)(p23;q23): found in M5a or M4 ANLL; the rare ALL cases of t(9;11) are most often found in infants; infants cases (<1 year) account for 15% of all t(9;11) cases; med EFS: 1 year, 3 year EFS 20%; the gene involved in 9p22 is AF9.
- t(10;11)(p12;q23): rare; M4 or M5 ANLL; ALL at times; infants represent 40% of cases; the gene involved in 10p12 is AF10.
- t(11;19)(q23;p13.3): ALL, biphenotypic AL and M4 or M5 ANLL; half cases of t(11;19)(q23;p13.3) are infant cases; a study on 40 cases showed that med survival was 5 mths, with a 2 year survival of 20% (unpublished observation); the gene involved in 19p13.3 is ENL.
- Other 11q23 rearrangements are rarely found in infants leukaemias.
- In 11q23 sits MLL, which encodes a 431 kDa protein; contains two DNA binding motifs (a AT hook, and Zinc fingers), a DNA methyl transferase motif, a bromodomain; transcriptional regulatory factor; nuclear localisation; wide expression; homology with trithorax (drosophila); the fusion protein includes the N-term AT hook and DNA methyltransferase from MLL fused to (little or most of) the partner C-term part from the other chromosome.

Disease

t(1;22)(p13;q13)

Phenotype/cell stem origin

M7 ANLL.

Epidemiology

39 cases so far described; 6 (perhaps much less); the only leukaemia (nearly) restricted to infant cases; median age is 4 mths.

Clinics

Organomegaly, bone marrow fibrosis; misdiagnosis of a solid tumour is frequent.

Prognosis

Remission is obtained in only half cases, median survival is 7 mths.

Disease

12p abnormalities

Phenotype/cell stem origin

B lineage ALL mainly (CD10+); M5 ANLL at times.

Epidemiology

At least 9 cases.

Prognosis

No sufficient data.

Disease

inv(16)(p13q22)

Phenotype/cell stem origin

M4 ANLL.

Epidemiology

At least 3 cases reported.

Clinics

High WBC, CNS involvement.

Prognosis

Is very poor so far (remission duration: 0, 2, 6 mths), in contrast with the usual inv(16) prognosis.

Disease

t(5;15)(p15;q11)

Phenotype/cell stem origin

B lineage ALL.

Epidemiology

5 known cases.

Prognosis

Unknown; CR in 5/5.

Disease

t(8;16)(p11;p13)

Phenotype/cell stem origin

M5/M4 ANLL.

Epidemiology

At least 3 cases.

Prognosis

Survival: 0.5 mth, 22 mths+, 24 mths+.

Disease

+19 and/or +21

Phenotype/cell stem origin

ANLL and ALL.

Epidemiology

At least 5 cases.

Prognosis

No survival data available.

Disease

Other chromosome rearrangements: +8 (solely or not), found in a few cases, del(6q), t(1;19)(q23;p13), and non recurring anomalies, found in at least one case each; finally, the kayotype has been found to be normal in a percentage of cases.

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