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Leukaemia Section

Mini Review

t(8;14)(q24;q32), t(2;8)(p12;q24), t(8;22)(q24;q11)

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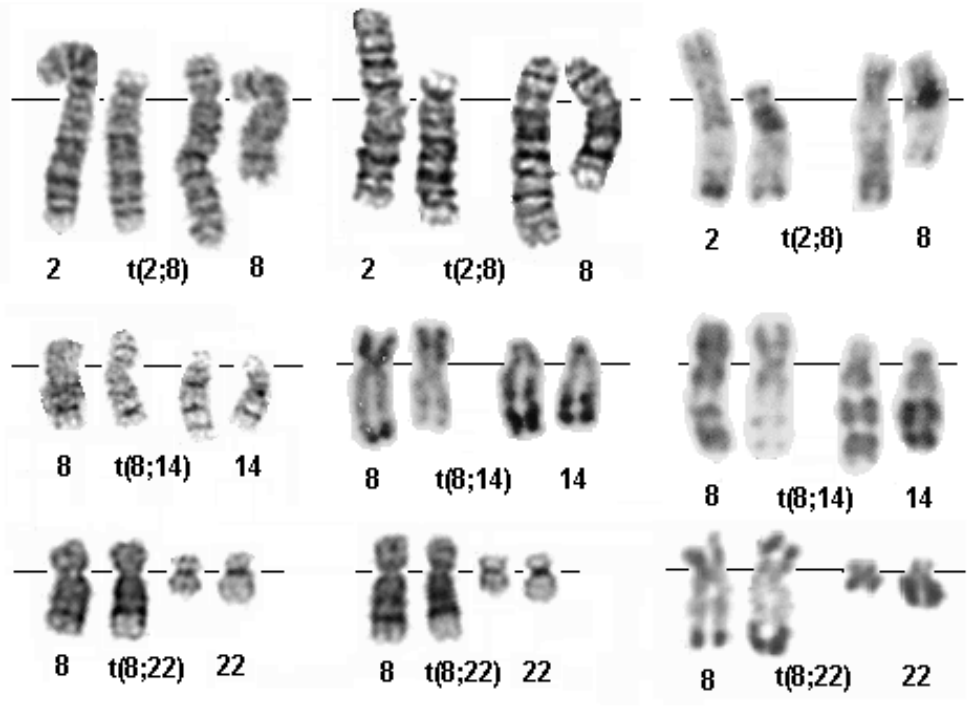
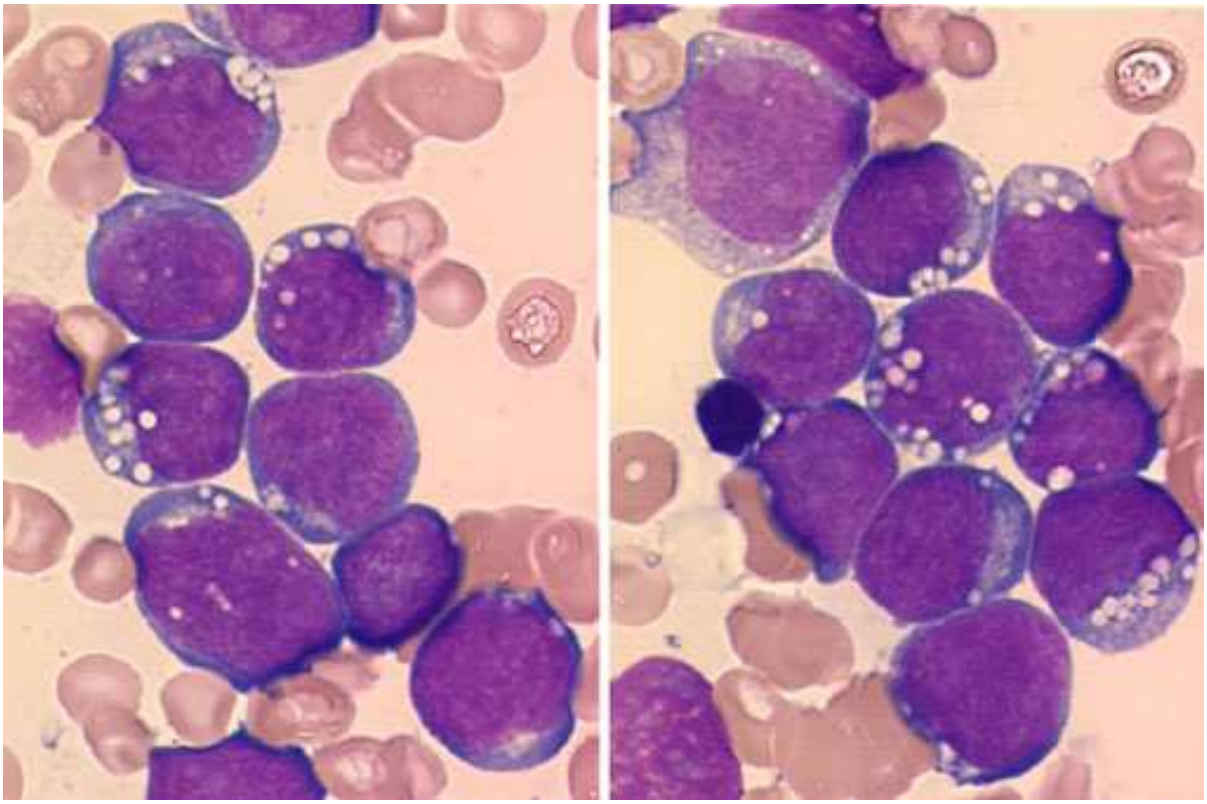
Identity

Note

The 3 translocations are variants of each other, and they share the same clinical significance.



Top row: t(2;8)(p12;q24) G- banding (left and center) - Courtesy Diane H.Norback, Eric B. Johnson, Sara Morrison-Delap; R- banding - (right) Courtesy Jean-Luc Lai.
Middle row: t(8;14)(q24;q32) G- banding - (left) Courtesy Diane H. Norback, Eric B. Johnson, Sara Morrison-Delap; R- banding - (center Courtesy Jean-Luc Lai; right: Editor).
Lower row: t(8;22)(q24;q11) G- banding (left and center) - Courtesy Diane H. Norback, Eric B.Johnson, Sara Morrison-Delap UW Cytogenetic Services ; R- banding - (right) Courtesy Jacques Boyer.



Bone marrow sample: the medium-sized cells show a diffuse monotonous pattern of infiltration. The nuclei are round, cytoplasm deeply basophilic and usually contain vacuoles. The morphological feature in this bone marrow smear (Giemsa), quite similar to tumor cells as seen in tissue imprints, is highly characteristic of Burkitt lymphoma - Courtesy Georges Flandrin.

Clinics and pathology

Disease

Described both in B-cell acute lymphoblastic leukemia (ALL) and in non-Hodgkin lymphomas (NHL), especially in the Burkitt lymphoma.

Phenotype/cell stem origin

B-cell malignant hemopathies.

Epidemiology

Of the lymphoma: the translocation is present in both the endemic African Burkitt lymphoma and in the non endemic tumor type (Europe, America, Japan); the L3-ALL represents only 2% of ALLs and is closer to a leukemic stage of a lymphoma than to other ALL types.

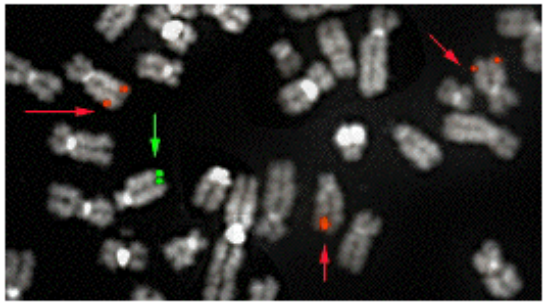
Cytology

ALL: L3 morphology according to the FAB classification, very occasionally L1 or L2 cytology reported.

Cytogenetics

Cytogenetics morphological

t(8;14) is described in 75-85% of the cases, t(2;8) in 5%, and t(8 ;22) in the remaining 10%; high-quality metaphases are required to detect t(8;14) and t(8;22).



944B18 The figure illustrates the translocation of the c-Myc gene (probe 944B18, red) to 14q32.3 - Courtesy Mariano Rocchi,

Additional anomalies

Reported in 70% cases, especially: structural rearrangements of the long arm of chromosome 1 (30% cases) resulting in a partial trisomy 1q, rearrangements of 13q34 (15% cases); a t(1;13)(q23;q34) has been described.

Variants

t(2;8)(p12;q24) and t(8;22)(q24;q11) are variants of the t(8;14)(q24;q32); three-way rearrangements and translocations of submicroscopic chromosome fragments have also been described.

Genes involved and proteins

Note

On the molecular point of view, in all these three translocations, the oncogene C-MYC is juxtaposed

either with the immunoglobulin heavy chain locus IGH (14q32), the kappa light-chain locus IGK (2p12), or the lambda light-chain locus IGL (22q11); all these translocations share a breakpoint in 8q24 (C-MYC locus).

C-MYC

Location

8q24

DNA/RNA

The human C-MYC oncogene is the cellular homologue of an avian retrovirus; in vertebrates, it belongs to a small gene family with closely related members (C-MYC, N-MYC, L-MYC); C-MYC has three exons; two promoters P1 and P2 control the C-MYC transcription; the choice of the promoter depends on the myc protein level. P2 promoter is considered as the most active promoter, generating a 2.25 kb transcript, whereas P1 promoter enrates a 2.4 kb transcript; the main part of 5' first exon corresponds to an untranslated region, MYC1 translation starting at a CUG codon near its 3' end, having 14 additional N-terminal amino-acids compared with MYC2 translation site localized 5' near the second exon beginning.

Protein

Myc protein is a transcription factor of the helix-loop-helix/leucine zipper family that activates transcription as obligate heterodimer with a partner protein, Max.

Immunoglobulin genes : IGH, IGK, IGL

Location

Located in 14q32, 2p12 and 22q11 respectively.

Result of the chromosomal anomaly

Hybrid gene

Note

No hybrid gene but the translocation of C-MYC close to enhancers constitutively active in this specific cell lineage.

Description

C-MYC is translocated to der(14) in the t(8;14), whereas it remains on der(8) in the variant translocations; t(8;14) leads to a head-to-head fusion of C-MYC with the heavy chain immunogloulin locus: 8q24 is close to the 5' extremity of C-MYC exon 2, leading the all translated gene region to 14q32; the 8q24 breakpoint region is variable, scattered over a 190 Kb region, 5' far from C-MYC or within C-MYC; the 14q32 breakpoint region is mainly located in the constant region, very close within the switch or joining regions; C-MYC juxtaposed to the immunoglobin constant regions and enhancer is overexpressed, shutting down the normal remaining C-MYC; in both t(2;8) and t(8;22), the breakpoint is in 3' of or distal to the C-MYC gene which always remains on der(8); the rearrangement with respectively Igk or Igl and C-MYC is head-to-tail.

Fusion protein

Note

The protein c-myc resulting from the translation of the second and third exons, through DNA- binding properties, plays a role in regulating cell growth and differentiation.

Oncogenesis

Constitutive expression of c-myc induces proliferation even in the absence of growth factors.

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