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Leukaemia Section

Mini Review

inv(16)(p13q22), t(16;16)(p13;q22), del(16)(q22)

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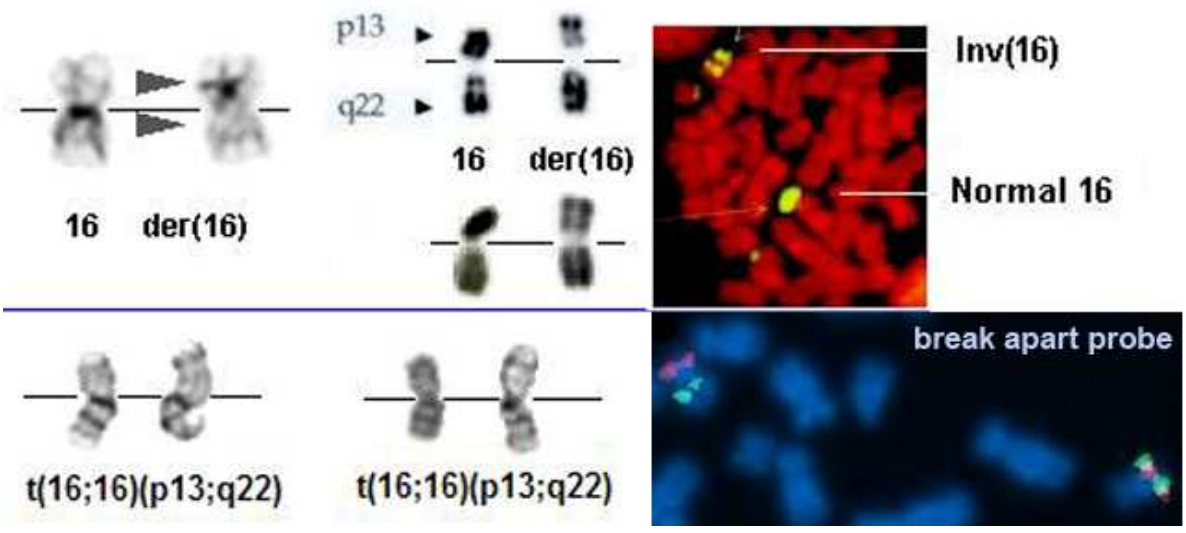
Identity

Note

The three chromosome anomalies are variants of each other, and they share identical clinical features and genetic pathogenesis.



inv(16)(p13q22) G- banding (left) - Courtesy Jean-Luc Lai and Alain Vanderhaegen; R- banding center bottom: - Courtesy Christiane Charrin, center top and FISH (top right) -Courtesy Pascale Cornillet-Lefebvre and Stephanie Struski; FISH (bottom right) - Courtesy Hossein Mossafa; commercial FISH probes, split in the inv(16). t(16;16)(p13;q22) G-banding - Courtesy Diane H. Norback, Eric B. Johnson, and Sara Morrison-Delap, UW Cytogenetic Services.

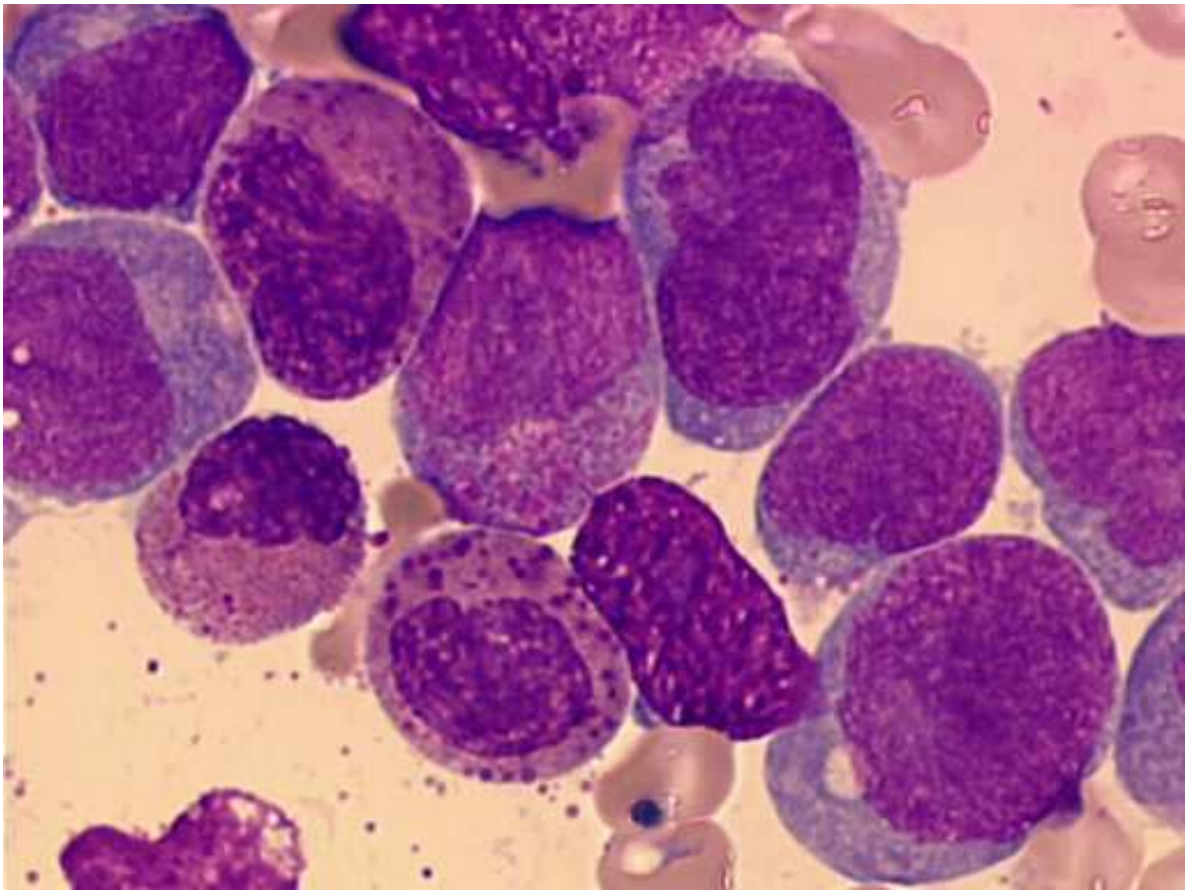
Clinics and pathology

Disease

Acute non lymphoblastic leukaemia (ANLL); myelodysplastic syndromes (MDS) at times.

Phenotype/cell stem origin

Nearly pathognomonic of M4eo-ANLL (all M4eo share the 16q22 anomaly -see also below-, but not all 16p13/16q22 are found in the M4eo subtype: i.e. this anomaly, although mainly found in M4-ANLL



Patients with inv(16) usually correspond to the subclass of AML M4, with a specific abnormal eosinophil component and is considered as a distinct entity in correlation with these specific chromosomal abnormalities. These cases of AML M4 are referred as AML M4EO. In addition to the morphological features of AML M4 excess of monocytes), the bone marrow shows a variable number of eosinophils at all stages of maturation without significant maturation arrest. The most striking abnormalities involve the immature eosinophilic granules. Those are mainly evident at the promyelocyte and myelocyte stages. The abnormalities are not usually evident at later stages of maturation. These eosinophilic granules are often larger than those normally seen in immature eosinophils, purple-violet in color and in some cells are so dense that they obscure the cell morphology - Courtesy Georges Flandrin, CD-ROM AML/MDS G.Flandrin/ICG. TRIBVN

with marked eosinophilia, may (rarely) been found in : M2 or M5, M4 without eo, or in MDS; there are also known cases of chronic myelogenous leukaemia in blast crisis (BC-CML) with a M4 eo phenotype and inv(16); found at times in treatment related ANLL; 3 cases of infant leukaemia so far described; note: CD2 (T-cell marker) may be co-expressed

Epidemiology.

5-10% of ANLL, 20% of M4.

Clinics

CNS involvement is frequent, according to some authors, in particular at relapse.

Cytology

Most often: eosinophils > 5%, with large immature basophilic granules, NASCA+, in the bone marrow (but normal in blood: this M4 do not show the eo' characteristic in blood).

Prognosis

High CR rate; better prognosis than most other ANLL; median survival may be 5 years.

Cytogenetics

Cytogenetics morphological

May be overlooked, especially with R-banding; best seen without banding procedure ('giemsa') for some workers.

Cytogenetics molecular

With 16p13 probes: as a deletion within 16p13 often accompany the 16p13/16q22 rearrangement (in 20% of cases), the split signal may be lost.

Additional anomalies

None 2/3 of cases; +8, +22 in 15% each, del(7q), +2; apparently without prognostic significance.

Variants

Are known:
1- t(16;16)(p13;q22); - del(16)(q22): may be associated with less typical phenotype and preceding MDS, older age, complex karyotype, worse prognosis;
2- but also: translocations of 16q22 with various partners in: t(1;16)(p31-32;q22), t(3;16)(q21;q22),

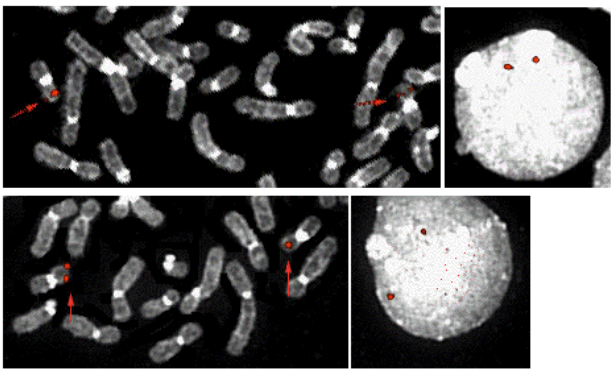
t(5;16)(q33;q22), associated with eosinophils anomalies.

Genes involved and proteins

MYH11

Location

16p13



c-MYH11 (16p13) in normal cells: PAC 1032E3 (top) and PAC 1179J13 (below) - Courtesy Mariano Rocchi.

Protein

Contains a N-term ATPase head responsible for actin binding and mechanical movement, and a C-term long repeat of coil-coil domain to facilitate filament aggregates; member of the myosin II family.

CBFb

Location

16q22

Protein

Subunit of the transcription factor complex CBF; CBFb by itself does not contain any DNA binding motif or transcriptional activation domain, but forms a dimer with CBFa: --> transcription factor.

Result of the chromosomal anomaly

Hybrid gene

Description

5' CBFb - 3' MYH11; breakpoint in CBFB intron n°5 and in MYH11 intron A (i.e. : 5)

Transcript

At least 8 different CBFb-MYH11 fusion transcripts have been described, transcript type A (with positions at nucleotides 495 and 1921 respectively) being found in about 90% of the patients; most breakpoints in MYH11 are also clustered; no reciprocal MYH11-CBFB transcript.

Fusion protein

Description

N-term - the first 165 (or 133 in a few cases) amino acids of CBFb, removing only 17 or 22 amino acids fused to the tail of MYH11 C-term with its multimerization domain; also variable breakpoint in MYH11; identical fusion protein in the cases of RAEBT and BC-CML.

Expression / Localisation

Nuclear localisation.

Oncogenesis

The fusion protein seems both to diminuish the quantity of active CBF and to compete with it, there is accumulation of CBFb-MYH11/CBFa multimeres in the nucleus.

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