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Leukaemia Section

Short Communication

t(12;18)(p13;q12)

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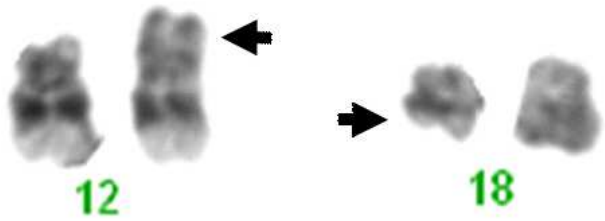
Identity

Note

The balanced translocation between the short arm of chromosome 12 and the long arm of the chromosome 18 -t(12;18)(p13;q12)- has been described in a patient with acute myeloid leukemia secondary to myelodysplastic syndrome. The key event in the t(12;18)(p13;q12) involving ETV6 is the overexpression of SETBP1 (18q12), a gene located close to the breakpoint (Cristobal et al., 2010).



Partial karyotype of a patient with AML-M5 and a t(12;18)(p13;q12). Derivative chromosomes are indicated by arrows.

Clinics and pathology

Disease

Acute Myeloid Leukemia (AML-M5) secondary to Myelodysplastic Syndrome (MDS).

Epidemiology

This is a rare chromosomal rearrangement, characterized at molecular level in only one AML patient to date.

Clinics

A 76-year-old caucasian man was diagnosed with myelodysplastic syndrome (MDS).

Disease evaluation of the patient 3 years after the diagnosis showed anorexia, perspiration and loss of 7 kg.

Cytology

Blast morphology was indicative of acute monocytic leukemia.

Pathology

Bone marrow aspirate was hypercellular, showing 80% blasts.

Treatment

The patient received standard induction chemotherapy for two months, and had partial remission at the next evaluation.

Evolution

The patient relapsed 2 months later and, eventually, died.

Prognosis

SETBP1 overexpression is a marker of poor prognosis in AML, with special relevance in the subgroup of elderly patients (Cristobal et al., 2010).

Genetics

Note

The t(12;18)(p13;q12) involves the ETV6 gene (12p13), a transcription factor frequently rearranged in both myeloid and lymphoid leukemias.

More than 15 ETV6 fusion gene partners have been described. Most translocations involving ETV6 generate fusion genes that lead to the activation of either unrelated transcription factors or kinases (Cools et al., 2002).

However, in some cases functionally significant fusions could not be identified and an alternative mechanism consisting in the ectopic expression of genes located close to the breakpoints has been described. This molecular mechanism, which has been described mainly in lymphoid leukemias and lymphomas, is an uncommon mechanism in myeloid leukemias, although some examples have been reported (Cools et al., 2002; Odero et al., 2002; Nucifora et al., 2006). The key event in the t(12;18)(p13;q12) involving ETV6 is the overexpression of SETBP1 (18q12), a gene located close to the breakpoint (Cristobal et al., 2010).

Cytogenetics

Cytogenetics morphological

t(12;18)(p13;q12) as the sole abnormality; +19 as an additional anomaly at relapse.

Cytogenetics molecular

FISH showed that the breakpoint on 12p13 was located between exons 2 and 3 of ETV6.
To confirm the position of the breakpoint on chromosome 18, BACs located at 18q12 were used as probes in FISH experiments. Analysis on BM cells of the patient showed that one signal hybridized to the normal chromosome 18, and the other split and hybridized to both der(18) and der(12). FISH showed that the breakpoint was located 5' and close to the SETBP1 gene.

Probes

The order of the probes on 18q12 is centromere-840B16-937P23-252G8-941F5-telomere.

To map the breakpoints bacterial artificial chromosomes obtained from the Roswell Park Cancer Institute (Buffalo, NY) were used and labeled with SpectrumGreen-dUTP or SpectrumOrange-dUTP.

Additional anomalies

The presence of a trisomy 19 in one clone suggests that SETBP1 overexpression, as a consequence of position effects, could cooperate with other additional aberrations to the development of AML in this patient.

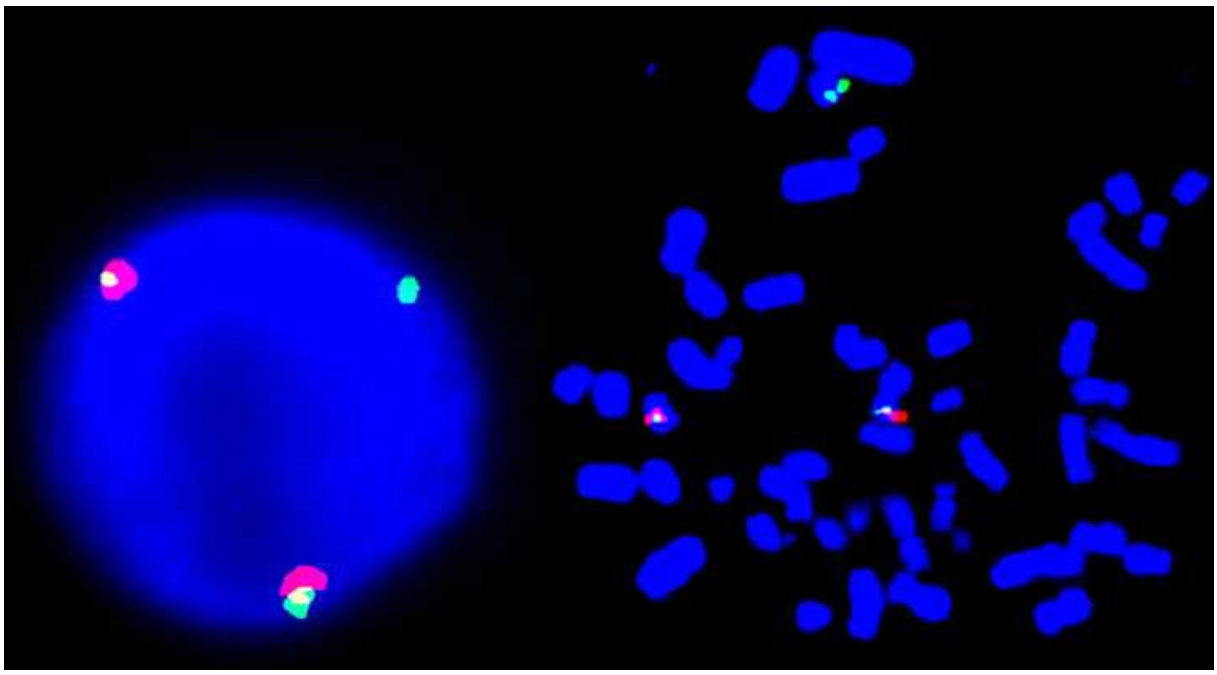
Genes involved and proteins

Note
The key event in the t(12;18)(p13;q12) involving ETV6 is the overexpression of SETBP1 (18q12), a gene located close to the breakpoint (Cristobal et al., 2010).

ETV6

Location
12p13

Protein
The ETV6 gene encodes a transcription factor frequently rearranged in both myeloid and lymphoid leukemias.
Translocations involving this gene mostly result in the generation of in-frame fusion genes between different domains of ETV6 and partner genes encoding either kinases or transcription factors with importance in cancer.
However, in some cases functionally significant fusions could not be detected, and the deregulation of the expression of oncogenes located close to the breakpoints has been described as an alternative leukemogenic mechanism (Cools et al., 2002).



FISH analysis indicating the breakpoint on 18q12: probe RP11-252G8 (green) splits and hybridizes in both der(18) and der(12).

SETBP1

Location

18q12

Protein

The SETBP1 gene encodes a protein of 1542 amino acids and a molecular weight of 170 kDa, with a predominantly nuclear location (Minakuchi et al., 2001; Cristobal et al., 2010).

The protein contains a region homologous to the dimerization domain of SKI, and a SET-binding region (Minakuchi et al., 2001).

The protein SET (I2PP2A/TAF-Iβ) inhibits PP2A, a phosphatase with a pivotal role in cancer as a tumor supressor (Mumby, 2007), through the phosphorylation of the PP2Ac tyrosine-307 (Li et al., 1996).

Interestingly, activation of SETBP1 expression by retroviral integration in hematopoietic progenitor cells has been reported to confer a growth advantage leading to clonal expansion (Ott et al., 2006). Moreover, it has been reported that SETBP1 overexpression protects SET from protease cleavage, increasing the amount of full-length SET protein, and leading to the formation of a SETBP1-SET-PP2A complex that results in PP2A inhibition, and therefore promotes the proliferation and expansion of leukemic cells (Cristobal et al., 2010).

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