Solid Tumour Section
Mini Review

Carcinoma with t(15;19) translocation
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Identity

Other names: Mediastinal carcinoma with chromosome translocation t(15;19); Midline carcinoma of children and young adults with NUT rearrangement; Midline carcinoma with t(15;19); Poorly differentiated carcinoma with t(15;19); Poorly differentiated thymic carcinoma; t(15;19) positive tumor.

Clinics and pathology

Disease
Carcinoma with t(15;19) translocation.

Phenotype stem cell origin
It has been suggested that tumor cells derive from early epithelial progenitor cells.

Embryonic origin
The majority of the cases presumably derive from various (midline) epithelial surfaces. One tumor, localized to the iliac bone and staining negative for epithelial, endothelial, germ cell and neuroendocrine markers has been reported, suggesting that the tumor might also derive from non-epithelial structures.

Etiology
Unknown.

Epidemiology
A total of 13 cases have been reported to date. All tumors occurred in children or young adults with a median age of 15 years of age (range 3-35). There seem to be no sex predilection (8 males, 5 females).

Clinics
The growth pattern is typically aggressive and locally invasive. Metastatic growth is common in particular in bone, but also in lymph nodes and lungs.

Cytology
Focal reactivity with pan-cytokeratin markers. Negative for CD30, CD45, PLAP, HMB45, S100 and neuroendocrine markers.

Pathology
The tumor cells are typically undifferentiated, of intermediate size and the mitotic index is high.

Treatment
Intensive combined chemotherapy and occasionally radiotherapy.

Prognosis
Extremely poor. Among the cases reported so far, the median survival time was 18 weeks (range 6-67). It has been suggested that a critical prognostic difference exists between BRD4-NUT/t(15;19) positive tumors and tumors where NUT is rearranged but fused to an as yet unknown partner.

Cytogenetics

Cytogenetics morphological
The characteristic t(15;19) has been observed in all reported cases. The reported breakpoints on chromosome 15 have varied (15q11-q15). The breakpoints on chromosome 19 clustered to 19p13 in the majority of the cases. In one case the breakpoint was interpreted as 19q13.

Cytogenetics molecular
Various FISH protocols for the detection of 15q and 19p rearrangements, strongly indicating the presence of a t(15;19), have been reported. The material used has been paraffin-embedded sections of tumor biopsy or metaphase spreads of cultured tumor tissue.
Carcinoma with t(15;19) translocation

Probes
Probes for NUT: RP11-194H7 covering the gene or BAC 87M17 and YAC 76E7 flanking the gene.
Probes for BRD4: RP11-637P24 covering the gene or BACs 1H8+64O3 and BACs 412E10+3D4 flanking the gene.

Additional anomalies
The t(15;19) is typically seen as the sole change. In one case a variant t(11;15;19) was reported.

Variants
t(15;?)(q14;?) leading to rearrangement and fusion of NUT to an unknown partner gene.

Genes involved and Proteins

NUT (nuclear protein in testis)

Location: 15q14 (position 32425358-32437221 on the chromosome 15 genomic sequence according to the UCSC database; assembly of May 2004)

DNA/RNA
The gene consists of 7 exons that span approximately 12 kb of genomic DNA in the centromere-to-telomere orientation. The translation initiation codon and the stop codon are predicted to exon 1 and exon 7, respectively. The corresponding wildtype mRNA transcript is 3.6 kb.

Protein
The open reading frame is predicted to encode a 1127 amino acid protein with an estimated molecular weight of 120 kDa. The protein is nuclear and Northern blot analysis has indicated that the normal expression of the NUT gene is highly restricted to the testis.

BRD4 (bromodomain containing 4)

Location: 19p13 (position 15252262-15209302 on the chromosome 19 genomic sequence according to the UCSC database; assembly of May 2004).

DNA/RNA
The gene consists of 20 exons that span approximately 43 kb of genomic DNA in the centromere-to-telomere orientation. The translation initiation codon and stop codon are located to exon 2 and exon 20, respectively. Two isoforms of BRD4 have been reported. The BRD4 long isofrom encodes a 6.0 kb mRNA that corresponds to the full length transcript. The BRD4 short isoform encodes a 4.4 kb mRNA that corresponds to an alternative splicing variant lacking exons 12-20.

Protein
The open reading frame encodes a 1362 amino acid protein with a molecular weight of 200 kDa. The protein is nuclear and Northern blot analysis has shown an ubiquitous normal expression of both BRD4 isoforms.

Result of the chromosomal anomaly

Hybride Gene
Description
The t(15;19)(q14;p13) results in a BRD4-NUT chimeric gene where exon 10 of BRD4 is fused to exon 2 of NUT.

Detection protocole
The hybrid gene can be visualized by FISH using gene specific probes or by RT-PCR.

Fusion protein
Description
The BRD4-NUT fusion protein is composed of the N-terminal of BRD4 (amino acids 1-720 out of 1372) and almost the entire protein sequence of NUT (amino acids 6-1127). The N-terminal of BRD4 includes bromodomains 1 and 2 and other, less well characterized functional domains.

Oncogenesis
It has been suggested that the oncogenic effect of the NUT-BRD4 fusion is caused not only by the abnormal regulation of NUT by BRD4 promotor elements but also by the consequent ectopic expression of NUT in non-germinal tissues.

References
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