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Solid Tumour Section

Mini Review

Soft Tissue Tumors: Low grade fibromyxoid sarcoma

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Identity

Alias

Hyalinizing spindle cell tumor with giant rosettes.

Note

Low grade fibromyxoid sarcoma is a rare, low-grade malignant soft tissue neoplasm with a potential for local recurrences as well as distant metastases.

Classification

Note

Low grade fibromyxoid sarcoma belongs to the group of fibroblastic/myofibroblastic soft tissue tumors. Two main subtypes have been recognized: classical low grade fibromyxoid sarcoma and low grade fibromyxoid sarcoma with giant collagen rosettes.

Clinics and pathology

Disease

Low grade fibromyxoid sarcoma (LGFMS)

Embryonic origin

Cellular origin unknown, but presumably of mesodermal derivation. Tumor cells show fibroblastic differentiation.

Etiology

Unknown. No known risk factors.

Epidemiology

Low grade fibromyxoid sarcoma is supposed to be rare, but as it is difficult to diagnose the true incidence is unknown. Patients of any age may be affected, and the male: female ratio is 1:1.

Clinics

Low grade fibromyxoid sarcoma usually presents as a painless mass, typically in the proximal extremities.

Pathology

Classical cases of LGFMS display a mixture of hypocellular, collagen-rich areas and more cellular, myxoid areas. A characteristic feature is the whorling growth pattern, often seen at the transition from hypocellular to more cellular, myxoid areas. Mitotic figures are rare. A subset of LGFMS shows focal collagen rosettes.

Treatment

The only consensus treatment for low grade fibromyxoid sarcoma is surgical excision.

Prognosis

When radically excised, the prognosis is usually good. However, local recurrences have been reported in approximately 10% of the cases, and distant spreading occurs in 5-10% of the cases.

Cytogenetics

Note

In the Mitelman Database of Chromosome Aberrations in Cancer (2004), 16 cases with clonal aberrations are included.

Cytogenetics Morphological

The chromosomal translocation t(7;16)(q33;p11) is a characteristic feature. A few cases contain a supernumerary ring as the sole chromosomal abnormality. Comparative genomic hybridization allowed to assess the chromosomal origin of a supernumerary ring chromosome in one case. The

analysis revealed gain of material from 7p14-pter, 7q31-q33, and 16p. FISH experiments using contigs of BAC clones were performed in two cases of low grade fibromyxoid sarcoma carrying a t(7;16) abnormality. The analysis revealed that the breakpoints were located within BAC clones RP11-388M20 (AC009088) in band 16p11.2, and RP11- 29B3 (AC022173) and RP11-377B19 (AC009263) in band 7q33; all the examined clones gave split signals on the derivative chromosomes 7 and 16. The FISH results for chromosome 7 identified a breakpoint region containing a single gene (LOC155008), which is homologous to Drosophila Bbf-2, encodes a B-ZIP transcription factor and named BBF2H7 (BBF2 human homolog on chromosome 7). The data for chromosome 16 suggested FUS as the other candidate target gene.

Probes

BAC clones RP11-388M20 (AC009088) and CTD-2594M1 in band 16p11.2.BAC clones RP11- 29B3 (AC022173), RP11-377B19 (AC009263) and CTD-2375H21 in band 7q33.

Genes involved and proteins

Note

The t(7;16)(q33;p11) in two cases of low grade fibromyxoid sarcoma fuses the FUS gene to CREB3L2 (also named BBF2H7), a previously uncharacterized gene that is homologous to the Drosophila Bbf-2 gene. A further study of 59 low grade soft tissue tumors provided results indicating that this fusion gene is specific for LGFMS; all 12 fusion-positive cases in that series fulfilled the morphologic criteria for LGFMS, suggesting that reverse transcriptase polymerase chain reaction (RT-PCR) analysis for the detection of a FUS/CREB3L2 chimeric transcript may be a valuable tool in the differential diagnosis.

CREB3L2

Location

7q34

Note

Alternate symbols: BBF2H7, DKFZp586F2423, DKFZp686O19165.

DNA / RNA

The entire CREB3L2 gene spans more than 120 kb genomic DNA and is composed of 12 exons. Exon 1, containing the initiation codon ATG, is the largest (454 bp), and exon 7 the smallest (59 bp). Exon 12 includes the termination TAA codon. Introns 1 and 9 are the largest (73132 bp) and smallest (281 bp), respectively. Using in silico analysis and RT-PCR methodology analysis, a 2400 bp cDNA was compiled containing a 1560 bp open reading frame by Storlazzi et al. (2003). RT-PCR analysis on cDNAs from 24 human tissues showed that CREB3L2 is expressed in most of the examined tissues. The strongest expression was found in placenta, lung, spleen and intestine, and the weakest in heart, brain, skeletal muscle, thymus, colon and leukocytes. In fetal tissues, the weakest expression was detected in brain and heart. A splice variant, lacking exon 2, was found in placenta, spleen and fetal liver. Since northern blot analysis was not performed, the possibility of additional splice variants and the actual size of the normal CREB3L2 transcript is not determined yet. The cDNA clones with accession numbers BX649143 and BX648300 (5381 bp) indicate that the CREB3L2 mRNA might be longer than 7 kbp.

Protein

The 1560 bp open reading frame is coding for a 519 amino acid protein with an estimated molecular weight of 57 kDa. The amino acid sequence spanning residues 291-356 of the predicted human CREB3L2 protein contains a consensus B-ZIP domain highly similar to that in the CREB3L1 (OASIS), CREB3L3 (CREB-H), CREB3L4 (CREB4 or AIBZIP), CREB3 (LUMAN) and Drosophila Bbf-2 transcription factors with 80, 60, 9, 56 and 71% identity, respectively. It also contains the amino acid sequence RRKKKEY that is exactly conserved among CREB, CREM, ATF1, ATF6 and CREBL1. The leucine zipper motif of BBF2H7 is similar to that in CREB-H and CREB4 (pattern L-X6-C-X6-L-X6-L-X6-L-X6-L; Fig. 5). It contains six repeats and consists of five leucines and one cysteine at the second heptad position (amino acid 328) of the leucine zipper. Downstream of the B-ZIP domain, CREB3L2 also contains a hydrophobic region, which was predicted to be an a-helical transmembrane domain (position 376-397; GTCLMVVVLCFAVAFGSFFQGY). This structural feature is also seen in the other members of the family, i.e. OASIS, CREB-H, CREB3 and CREB4.

FUS

Location

16p11

Note

Alternate symbols are: TLS, FUS1. The FUS gene is also rearranged in myxoid liposarcoma with t(12;16)(q13;p11), which leads to its fusion with DDIT3. In acute myeloid leukaemia with t(16;21)(p11;q22) and in Ewing sarcoma with t(16;21)(p11;q22) as well, FUS is fused to the ERG gene, and in angiomatoid fibrous histiocytoma FUS is fused to ATF1.

Result of the chromosomal anomaly

Hybrid Gene

Note

Up to now, FUS/CREB3L2 chimeric transcripts were identified in 14 cases. The fusion points varied within

FUS, but clustered to exons 5, 6 and 7. Small intronic insertions were also seen at the junction. In CREB3L2, all the fusion points have been found within exon 5.

Detection

A detailed description of the RT-PCR protocols for analysis of FUS/CREB3L2 transcripts has been reported.

Fusion Protein

Note

The function of the FUS/CREB3L2 chimera is unknown but it is reasonable to assume that it will have similar consequences as the other FUS chimeric proteins in the cell. Thus, the B-ZIP-encoding domain of CREB3L2 comes under the control of the FUS promoter, which, in turn, may cause deregulation of genes normally controlled by CREB3L2. In addition, by fusing the B-ZIP domain of CREB3L2 to the N terminal part of FUS, the ability to dimerize with other members of the OASIS family could be affected. The FUS/CREB3L2 chimera might retain the ability, as do FUS/DDIT3 and FUS/ERG, to bind to RNA polymerase II via the N-terminal part of FUS but would lack the ability to recruit the transcription and translation factor Y-box binding protein-1 (YB-1) because of the replacement of the central and C-terminal parts of FUS by CREB3L2. Consequently, RNA splicing mediated by YB-1 also would be expected to be inhibited.

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