Myxoinflammatory fibroblastic sarcoma (MIFS) with t(1;10)(p22;q24)

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Identity

Other names
MIFS was originally described as acral MIFS (Meis-Kindblom and Kindblom, 1998).

Note
MIFS is an intermediate malignant soft tissue tumor usually located in the subcutaneous tissue of distal extremities (Kindblom et al., 2002).

Distant metastases are rare but the tumor has a propensity for multiple local recurrences. An identical t(1;10)(p22;q24) has been found in MIFS and hemosiderotic fibrolipomatous tumor (HFLT) (Hallor et al., 2009; Antonescu et al., 2011). HFLT is an intermediate malignant tumor of uncertain differentiation, morphologically distinct from MIFS. In similarity with MIFS, HFLT has a predilection for superficial soft tissue of distal extremities and present frequent local recurrences.

Despite their usually distinct morphology, there are tumors with mixed HFLT/MIFS histology (Elco et al., 2010).

These tumors also show a t(1;10) and suggest that there are either different morphological variants or different levels of tumor progression of a sole biological entity (Antonescu et al., 2011).

Classification

Note
MIFS is an intermediate malignant fibroblastic/myofibroblastic soft tissue tumor.

Clinics and pathology

Disease
Myxoinflammatory fibroblastic sarcoma (MIFS)

Phenotype / cell stem origin
The origin of the tumor cells is unknown. Their fibroblastic/myofibroblastic differentiation indicates that they derive from a mesenchymal precursor.

Etiology
Unknown.

Epidemiology
MIFS is a rare soft tissue tumor which primarily affects adults without any gender predilection.

Clinics
MIFS is an intermediate malignant tumor that usually presents as a slowly-growing, poorly-delineated mass of the superficial soft tissue of distal extremities (Kindblom et al., 2002). It is sometimes associated with pain and decreased mobility. In many cases the growth has been noted for a relatively long period of time before diagnosis. MIFS may be confused with inflammatory or post-traumatic lesions, benign or other malignant soft tissue tumors. Local recurrences are common but distant metastases are very rare.

Pathology
MIFS show a poorly delineated, multinodular growth pattern with alternating myxoid and cellular areas (Kindblom et al., 1998). There is a prominent
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inflammatory infiltrate that may obscure the neoplastic cells and cause misdiagnoses of a reactive or inflammatory process. Tumor cells, including large polygonal and bizarre ganglion-like cells with prominent inclusion-like nucleoli and variably sized, multivacuolated lipoblast-like cells, may be scattered singly or form coherent clusters.

Treatment
The treatment for MIFS is surgical excision.

Prognosis
Local recurrences are common and their incidence may depend on primary surgical treatment; multiple local recurrences may require eventual amputation (Kindblom et al., 2002). Distant metastases are, however, exceedingly rare.

Genetics
Note
MIFS, HFLT and tumors with mixed MIFS/HFLT histology share the same genetic aberrations; t(1;10) and amplification of a region in proximal chromosome arm 3p (Antonescu et al., 2011).

Cytogenetics

Cytogenetics Morphological
The majority of cytogenetically analyzed MIFS present a t(1;10)(p22;q24), or variants thereof (Mitelman Database of Chromosome Aberrations in Cancer 2012). Ring and/or giant marker chromosomes as well as aberrations involving chromosome 3 are also associated with this disease.

Cytogenetics Molecular
Fluorescence in situ hybridization analyses, using probes flanking the genes TGFBR3 in chromosome 1 and MGEA5 in chromosome 10, can be used as a diagnostic molecular test for MIFS and HFLT (Antonescu et al., 2011). Amplification of material from chromosome arm 3p can be detected by fluorescence in situ hybridization analyses and/or array-based genomic copy number analyses (Hallor et al., 2009).

Partial karyotype with a t(1;10)(p22;q24) and rearrangement of 3p.

Fluorescence in situ hybridization, using probes flanking the TGFBR3 and MGEA5 genes, respectively, can be used to detect the t(1;10)(p22;q24). A normal chromosome 10 show signals from probes located on either side of MGEA5 (labeled in red and yellow). On the der(10)t(1;10) the proximal probe (yellow) is detected while the more distal probe (red) is deleted.
DNA copy number analysis of a MIFS using array comparative genomic hybridization. A genome-wide copy number profile displays tumor/reference log2 ratios across the genome (top). Individual chromosomes are separated by vertical bars and chromosome 3 is labeled in yellow. The profile shows amplification of material from chromosome 3 and a few additional aberrations. Enlarged view of chromosome 3 shows two separate amplicons, the more proximal of these contains the VGLL3 gene (bottom).

**Genes involved and proteins**

**Note**
The breaks in chromosomes 1 and 10 seem to occur in, or close to, the genes TGFBR3 and MGEA5, respectively, and the translocation juxtaposes FGF8 in chromosome 10 with TGFBR3 in chromosome 1 (Hallor et al., 2009).

FGF8 is highly expressed, likely as a result of the rearrangement, in tumors affected by the translocation. Ring and giant marker chromosomes in MIFS contain amplified material from chromosome 3.

The core amplicon harbors the gene VGLL3, which is also highly expressed in affected tumors (Hallor et al., 2009).

This abnormality is, however, not specific for MIFS/HFLT and have been found in additional sarcomas as well as other malignancies (Hélias-Rodzewicz et al., 2010).

**VGLL3**

**Location**

3p12
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Fluorescence in situ hybridization analyses suggest that TGFBR3 is translocated from chromosome 1 and positioned in opposite direction next to the MGEA5 gene on the der(10)t(1;10) (Hallor et al., 2009).

**Note**
Amplification and high expression of VGLL3 in chromosome 3 is found in MIFS and HFLT as well as other sarcomas.

**DNA / RNA**
VGLL3 is a protein coding gene located at position 86987119-87040269 in chromosome 3 (http://www.ensembl.org; human assembly GRCh37). There are three transcript variants of this gene. The most extensive variant (transcript variant 1) comprises 10400 base pairs and consists of 4 coding exons.

**Protein**
VGLL3 encodes the protein vestigial like 3 (Drosophila). Translation of VGLL3 transcript variant 1 results in a 326 amino acid protein. There is not much known about the function of this protein. However, it is believed that mammalian vestigial like proteins could be involved in regulating members of the TEAD transcription factor family (Vaudin et al., 1999; Maeda et al., 2002).

**FGF8**

**Location**
10q24

**Note**
The translocation between chromosomes 1 and 10 juxtaposes FGF8 in chromosome 10 with TGFBR3 in chromosome 1. In tumors affected by the translocation, FGF8 is highly expressed.

**DNA / RNA**
FGF8 is a highly conserved gene located at position 103530081-103535827 in chromosome 10 (http://www.ensembl.org; human assembly GRCh37). There are six transcript variants of this gene and the alternating splicing results in products of 4-6 exons, which in turn encode proteins of 204-244 amino acids. The expression of FGF8 is controlled by several regulatory sequences located both upstream and downstream of the gene (Beermann et al., 2006; Inoue et al., 2006).

**Protein**
Fibroblast growth factor 8 belongs to the large family of fibroblast growth factors. Members of this family are secreted molecules which by activating their receptors are involved in a variety of biological processes (Thisse and Thisse et al., 2005). FGF8 is transcriptionally silent in most normal adult tissues. However, upregulation of this gene has been associated with tumor growth and has been identified in carcinomas of the breast, prostate, and ovary, as well as in synovial sarcoma (Tanaka et al., 1998; Ishibe et al., 2005; Mattila et al., 2007).

**Result of the chromosomal anomaly**

**Hybrid Gene**

**Note**
The t(1;10) juxtaposes FGF8 in chromosome 10 with TGFBR3 in chromosome 1 and the rearrangement is associated with high expression of FGF8 (Hallor et al., 2009).

**Description**
The translocation does not result in a conventional fusion gene. The functional outcome of the recurrent aberration seems to be high expression of the gene FGF8 (Hallor et al., 2009). The consistent involvement of TGFBR3, but lack of fusion transcripts, suggest that regulatory sequences in TGFBR3 are crucial for malignant transformation.

**Transcript**
Rearrangements of TGFBR3 and MGEA5.

**Detection**
Fluorescence in situ hybridization analysis using probes flanking the TGFBR3 and MGEA5 genes can be applied as a molecular test for detecting rearrangements of the genes (Antonescu et al., 2011).

**References**


This article should be referenced as such: