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Solid Tumour Section

Review

Angiomatoid fibrous histiocytoma (AFH)

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Identity

Other names: Angiomatoid malignant fibrous histiocytoma (AMFH)

Classification

Note: Angiomatoid fibrous histiocytoma is a rare soft tissue tumor of low-grade malignancy that usually occurs in children and young adults. Eighty-eight percent of patients are 30 years of age or younger. Enzinger in 1979 first designated the tumor as angiomatoid malignant fibrous histiocytoma. The tumour was later renamed angiomatoid fibrous histiocytoma because of its slow growth and rare metastasis.
This tumor forms solid, lobulated sheets of plump to spindled cells having histiocytic features adjacent to areas of haemorrhage.

Clinics and pathology

Note: This tumour typically affects children and young adults, presenting as a painless, slowly growing subcutaneous soft tissue mass that is usually located in the extremities and less commonly in the trunk, head, and neck. Only 18% of reported cases involved deep structures, such as skeletal muscle or periosteum.

Disease

Symptoms of anemia, weight loss, and fever are observed in a minority of cases; local symptoms, such as pain or tenderness, are extremely rare.

Embryonic origin

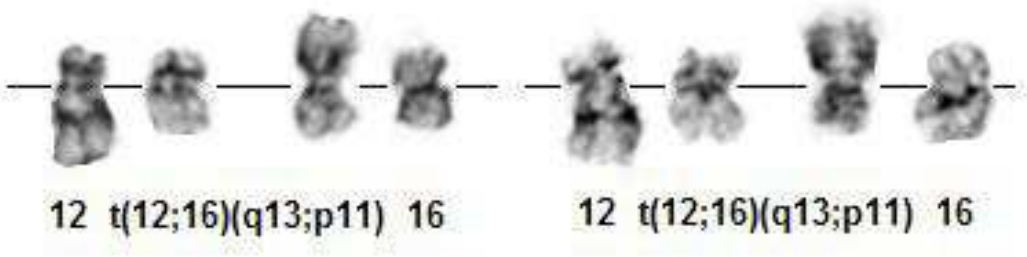
The cell of origin of AFH remains unclear. It is probably that AFH arises from a pluripotent mesenchymal cell due to ultrastructural morphology supports histiocytic, vascular, smooth, and striated muscle differentiation.

Clinics

Clinically, the tumor is often mistaken for hematoma or hemangioma. The diagnosis of angiomatoid fibrous histiocytoma is made on the basis of histopathology and immunohistochemical studies. Three microscopic findings are characteristic of AFH: (1) solid arrays or nests of histiocyte-like cells, (2) hemorrhagic cyst-like spaces, and (3) aggregates of chronic inflammatory cells. Multifocal recent and old hemorrhages are a striking feature in this tumor. These spaces resemble vascular spaces, but they are not lined by endothelium. Inflammatory cells present include lymphocytes and plasma cells. A thick pseudocapsule and occasional germinal centers give this tumor a resemblance to a lymph node.
Immunohistochemical studies are helpful in differential diagnosis of AFH. It was reported that the histiocytic marker CD68 was positive in 9 of 19 (47%) cases of angiomatoid fibrous histiocytoma. Immunopositivity for myoid or myofibroblastic markers in more than 50% of cases has also been reported.

Treatment

Local recurrence has been reported in 11% of patients and distant metastasis in 1%; wide excision is recommended as the treatment of angiomatoid fibrous histiocytoma. Local recurrence is attributed to the infiltrative margin and deep location of the tumour. Angiomatoid fibrous histiocytoma in the head and neck also can frequently recur, which may be a result of the difficulty of performing a wide local excision. If the tumor is unresectable or has metastasized, adjuvant chemotherapy may be helpful.



t(12;16)(q13;p11) G- banding - Courtesy G. Reza Hafez, Eric B. Johnson, and Sara Morrison-Delap.

Cytogenetics

Note: This disease is characterised by the translocations: t(12;16)(q13;p11) and t(12;22)(q13;q12).

Cytogenetics molecular

FUS-ATF1 fusion gene in the t(12;16)(q13; p11).
EWSR1-ATF1 fusion gene in the t(12;22)(q13;q12).

Genes involved and Proteins

FUS (TLS)

Location: 16p11

DNA/RNA

FUS gene consists of 15 exons located within 11 kb of genomic DNA.

Protein

FUS protein, provisionally designated TLS (translocated in liposarcoma), and then called FUS, contains an RNA-recognition motif and is a component of nuclear riboprotein complexes. Lack of FUS in mice causes lethality into neonatal period, it influences lymphocyte development in a non-cell-intrinsic manner, it has an intrinsic role in the proliferative responses of B cells to specific mitogenic stimuli, and it is required for the maintenance of genomic stability. The involvement of a nuclear riboprotein in these processes in vivo indicates that FUS is important in genome maintenance.

Somatic mutations:

FUS has been also shown a partner of gene fusions linked in other malignancies: fused to ERG in acute myeloid leukaemia with t(16;21)(p11;q22), fused to CREB3L2 in low-grade fibromyxoid sarcoma (LGFMS) by a translocation between chromosome bands 7q33-q34 (CREB3L2) and 16p11 (FUS), fused to ATF1 in histiocytoma or fused to CHOP gene in Myxoid Liposarcoma with t(13;16)(q13;p11).

ATF1

Location: 12q13

DNA/RNA

816 bp mRNA

Protein

ATF1 gene encodes a member of the CREB-ATF basic leucine-zipper (bZIP) family of transcription factors. This protein of 271 amino acids has a nuclear localization. Function: DNA binding protein, binds the consensus sequence: 5'GTGACGT (A/C) (A/G)-3'; cAMP-inducible transcription factor (cAMP-responsive enhancer-binding protein (CRE), like CREB. Is a member of the CREB protein family.

Somatic mutations:

t(12;22)(q13;q12) in Angiomatoid Fibrous histiocytoma ATF1-EWSR1. It is also rearranged in clear cell sarcoma (CCS) with t(12;22) (q13;q12), creating an EWSR1-ATF1 fusion gene.

EWSR1

Location: 22q12

DNA/RNA

DNA spans over 40 kb; open reading frame: 2.0 kb, 17 exons. Transcription 2.4 kb mRNA; centromere to telomere direction; differential splicing.

Protein

656 amino acids; serine-tyrosine tandem repeats. It has a wide expression and functions as a RNA binding.

Somatic mutations:

Ewing tumours with: t(11;22)(q24;q12) → FLI1 - EWSR1. Ewing tumours: including Ewing's Sarcoma and periphral primitive neuroectodermal tumour.
Ewing tumours with t(21;22)(q21;q12) → ERG - EWSR1. Ewing tumours (Ewing's Sarcoma and peripheral primitive neuroectodermal tumour).
Ewing tumours with t(7;22)(p22;q12) → ETV1 - EWSR1. Ewing tumours (Ewing's Sarcoma and peripheral primitive neuroectodermal tumour).
Ewing tumours with t(17;22)(q12;q12) → E1AF - EWSR1. Ewing tumours (Ewing's Sarcoma and peripheral primitive neuroectodermal tumour).
t(11;22)(p13;q12) / Intra abdominal desmoplastic small round cell sarcoma (IADSRCT) → WT1 - EWSR1.
t(12;22)(q13;q12) / Angiomatoid Fibrous Histiocytoma → ATF1 - EWSR1.
t(9;22)(q22;q12) / Myxoid Chondrosarcoma → TEC - EWSR1.

Result of the chromosomal anomaly

Hybride Gene

Description

FUS-ATF1 fusion gene t(12;16)(q13;p11).
EWSR1-ATF1 fusion gene t(12;22)(q13;q12).

Fusion protein

FUS/ATF-1

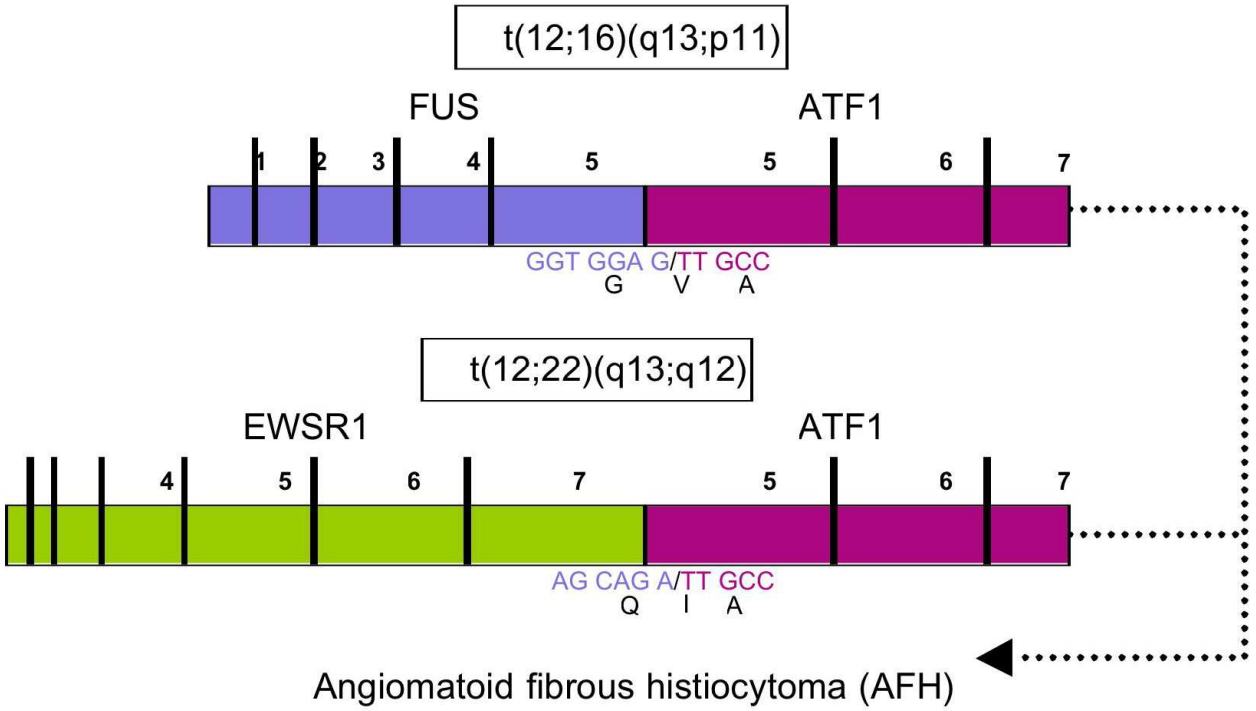
Description

The fusion gene contains the N-terminus of FUS and the DNA binding domain of ATF-1 with a glycine to valine transition at the junction. This is similar to the EWS/ATF1 chimeric protein found in CCS (clear cell sarcoma).
The normal ATF1 gene is transcribed from centromere to telomere, while the transcription of FUS seems to proceed in the opposite direction. Hence, the formation of FUS/ATF-1 is possible only if another genomic aberration, such as an inversion, occurs in addition to the chromosomal translocation. Such an event would be analogous to the formation of EWS/ERG in Ewing sarcoma and EWS/CHOP in myxoid liposarcoma.

EWSR1-ATF1

Description

See the diagram below. EWSR1 is interrupted at codon 265 (exon 7) and fused to codon 110 (exon 5) of ATF-1, resulting in an in-frame junction. The chimaeric protein is composed of the N-terminal domain of EWS linked to the bZIP domain of ATF-1.
The fusion gene EWSR1-ATF1 can be associated with different tumor types (Clear cell sarcoma (CCS) and Angiomatoid fibrous histiocytoma (AFH)). Activation of the EWSR1-ATF1 oncogene is probably an early step in the transformation process, but the overall gene expression patterns are likely to vary considerably between AFH and CCS, in keeping with their clinopathologic differences.
EWS/ATF1 functions as a potent constitutive activator of several cAMP-inducible promoters when assayed by transfection in cells lacking EWS/ATF1.
EWSR1 like FUS is an RNA-binding protein. Both are involved as the N-terminal part of fusion proteins in a number of sarcomas in combination with various transcription factor partners suggested to be tumor-specific.
It has been previously shown that the N-terminal parts of EWSR1 and FUS are fused to certain transcription factors, resulting in a common or very similar oncogenic potential having the same tumor phenotype.



This fusion was generated by a translocation between chromosomal bands 16p11 and 12q 13, harbouring the FUS and ATF1 genes, respectively. FUS is interrupted at codon 175 (exon5) and fused to condon 110 (exon 5) of ATF1, resulting in an in-frame junction with a glycine to valina (GGT to GTT) transition.

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