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Solid Tumour Section

Review

Soft Tissues: Extraskeletal myxoid chondrosarcoma

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Abstract

Review on Extraskeletal myxoid chondrosarcoma, with data on clinics, and the genes involved.

Keywords

Soft tissue tumor; Extraskeletal myxoid chondrosarcoma; NR4A3; EWSR1; TFG; TCF12; TAF15; FUS; HSPA8

Identity

Phylum

Soft Tissues: Tumors:Uncertain differentiation: Extraskeletal myxoid chondrosarcoma

Classification

Extraskeletal myxoid chondrosarcoma is characterized by a lobulated architecture (A), with a reticular growth pattern of interconnecting uniform tumor cells having ovoid-to-spindled nuclei and eosinophilic cytoplasm (B).

Clinics and pathology

Disease

Malignant mesenchymal neoplasm of uncertain differentiation.

Epidemiology

Extraskeletal myxoid chondrosarcoma is a rare tumor, encompassing 2.3% of soft tissue sarcomas in a Japanese series. Mean ages reported in various series range from 46 to 57 years. Males are affected about twice as often as females.

Clinics

Location: deep soft tissues of the lower extremities in about 75% of the cases, especially the thigh, the popliteal fossa, and the buttock, and can also occur in the trunk, abdomen, and head and neck.

Pathology

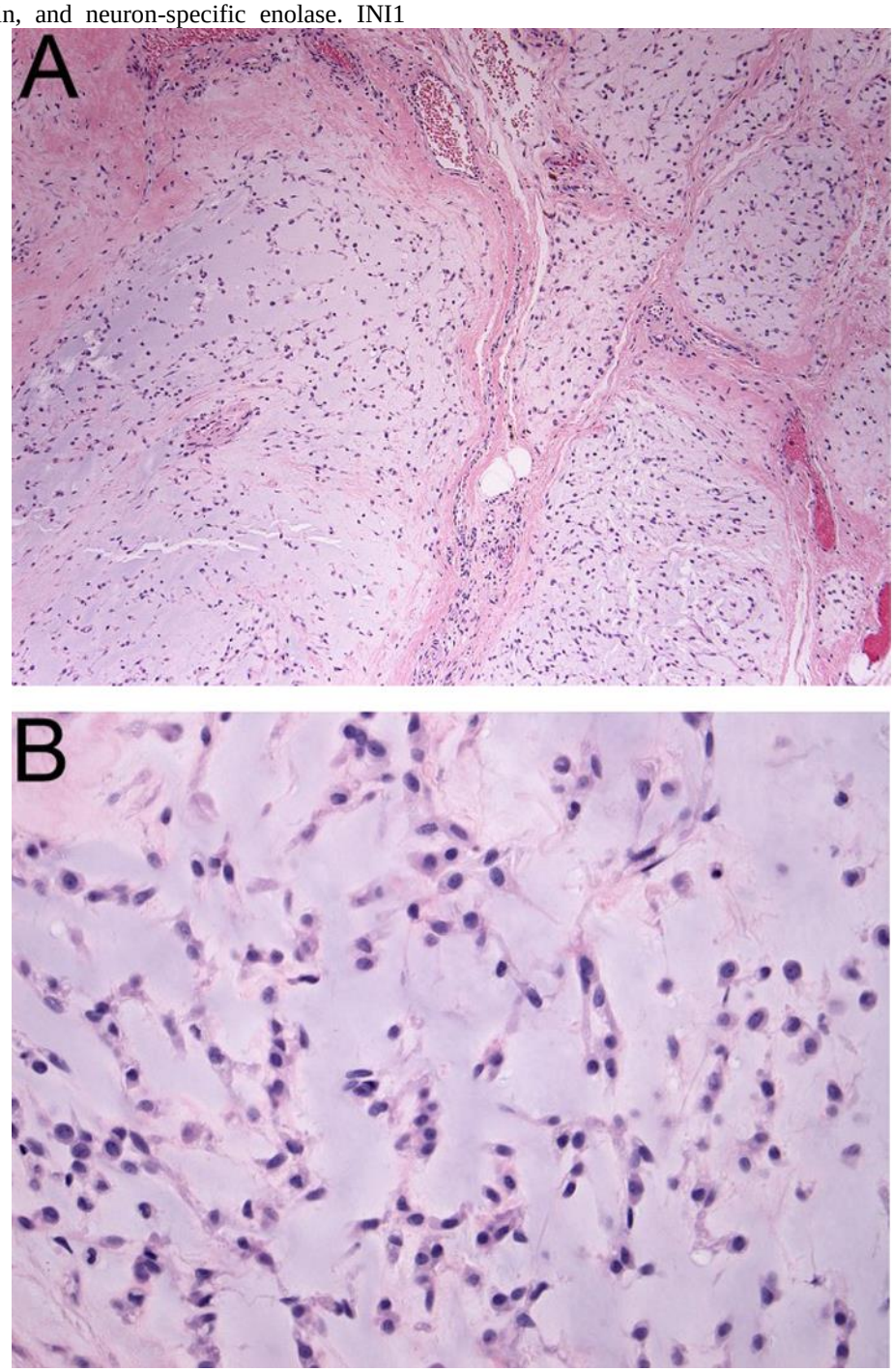
Macroscopic findings: the tumor presents as lobulated or multinodular mass, generally well circumscribed with pseudocapsule. The size of the tumor at the time of diagnosis may vary from 1 to about 20 cm (median size 7 cm).

Histology: Lobulated architecture with uniform round to spindled cells forming interconnecting cords, clusters, or trabeculae in a background of myxoid matrix. The tumor cells have variably eosinophilic or vacuolated cytoplasm that extends to

form the reticular growth pattern. A subset of tumors shows hypercellularity, higher grade cytomorphology, and epithelioid or rhabdoid features.

A subset of tumors is positive for S100, CD117, synaptophysin, and neuron-specific enolase. INI1 loss is observed in a subset, often with rhabdoid features.

Ultrastructurally, at least one third of the tumors demonstrate microtubular aggregates within dilated rough endoplasmic reticulum.



Extraskeletal myxoid chondrosarcoma is characterized by a lobulated architecture (A), with a reticular growth pattern of interconnecting uniform tumor cells having ovoid-to-spindled nuclei and eosinophilic cytoplasm (B).

Treatment

Treatment: surgical excision, with possible adjuvant chemotherapy.

Prognosis

Prognosis: high rates of local and distant recurrence, including pulmonary metastasis, but with associated prolonged survival.

Cytogenetics

NR4A3 Gene Fusions in Extraskeletal Myxoid Chondrosarcoma
t(9;22)(q22;q12) EWSR1/NR4A3
t(3;9)(q12;q22) TFG/NR4A3
t(9;11)(q22;q24) HSPA8/NR4A3
t(9;15)(q22;q21) TCF12/NR4A3
t(9;16)(q22;p11) FUS/NR4A3
t(9;17)(q22;q11) TAF15/NR4A3

Left: Karyotype of extraskeletal myxoid chondrosarcoma with t(9;22)(q22;q12). Right: Fluorescence in situ hybridization demonstrating rearrangement of NR4A3 by break apart probe.

Cytogenetics Morphological

- Recurrent gene fusions involving NR4A3 on chromosome 9 are observed in the majority of extraskeletal myxoid chondrosarcomas. The most common fusion partner is EWSR1, resulting in t(9;22)(q22;q12) with fusion of the 5' aspect of EWSR1 with NR4A3.
- Uncommon gene fusion events involving NR4A3 with TAF15, TCF12, TFG, FUS, or HSPA8 have also been reported. These events result in t(9;17)(q22;q11), t(9;15)(q22;q21), t(3;9)(q12;q22), t(9;16)(q22;p11), or t(9;11)(q22;q24), respectively.
- The breakpoint involving NR4A3 frequently occurs in the 5' untranslated region, with the resultant fusion including the entire NR4A3 protein.
- In extraskeletal myxoid chondrosarcomas without NR4A3 fusion, tumors may harbor loss of SMARCB1 (INI1) by loss of function mutation or gene deletion.
- Extraskeletal myxoid chondrosarcomas without EWSR1-NR4A3 fusion may exhibit rhabdoid morphology and high grade pathological features.

Genes involved and proteins

TFG (TRK-fused gene)

Location
3q12.2

DNA / RNA
39.51 kb; 8 exons; 1.9 kb mRNA.

Protein
Putative signal transducer; positive regulator of I-kappaB kinase/NF-kappaB cascade.

NR4A3 (nuclear receptor subfamily 4, group A, member 3)

Location
9q22.33

DNA / RNA
Transcripts: 2.6 kb and 3.7 kb.

Protein
Steroid-thyroid hormone-retinoid receptor; transcriptional activator.

TCF12 (transcription factor 12)

Location
15q21.3

DNA / RNA
370 kb; 21 exons; 4 kb mRNA.

Protein
Transcription factor; a basic helix-loop-helix protein.

TAF15 (TAF15 TAF15 RNA polymerase II, TATA box binding protein (TBP)-associated factor, 68kDa)

Location
17q12

DNA / RNA
16 exons; alternative splicing; 2.2 kb bp mRNA.

Protein
RNA-binding protein; part of theTFIID and RNA polymerase II complex.

EWSR1 (Ewing sarcoma breakpoint region 1)

Location
22q12.2

DNA / RNA

17 exons; 2.4 kb mRNA.

Protein
RNA-binding protein; transcription repressor.

FUS (fusion involved in t (12;16) in malignant liposarcoma)

Location
16p11.2

DNA / RNA
15 exons; 1.6 kb mRNA.

Protein
RNA-binding protein.

HSPA8

Location
11q24.1

DNA / RNA
9 exons; 1.9 kb mRNA.

Protein
Heat shock protein.

SMARCB1 (SW1/SNF related, matrix associated, actin dependent regulator of chromatin B1)

Location
22q11.23

DNA / RNA
9 exons; 1.2 kb mRNA.

Protein
Core component of BAF complex.

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