

Solid Tumour Section

Mini Review

Soft tissue tumors: Embryonal rhabdomyosarcoma

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Published in Atlas Database: January 2009

Online updated version : <http://AtlasGeneticsOncology.org/Tumors/EmbryoRhabdomyoID5193.html>
DOI: 10.4267/2042/44651

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Identity

Note: Embryonal rhabdomyosarcoma (ERMS) refers to one subtype of the rhabdomyosarcoma family of soft tissue tumors. These are mesenchymal tumours related to the skeletal muscle lineage.

Classification

ERMS is one of two subtypes of rhabdomyosarcoma. The other major subtype is alveolar rhabdosarcoma (ARMS). Within the ERMS subtype, there are two histopathologic variants with superior outcome, botryoid and spindle cell. Another proposed histologic variant is anaplastic ERMS. There are no genetic subtypes of ERMS with clinical significance.

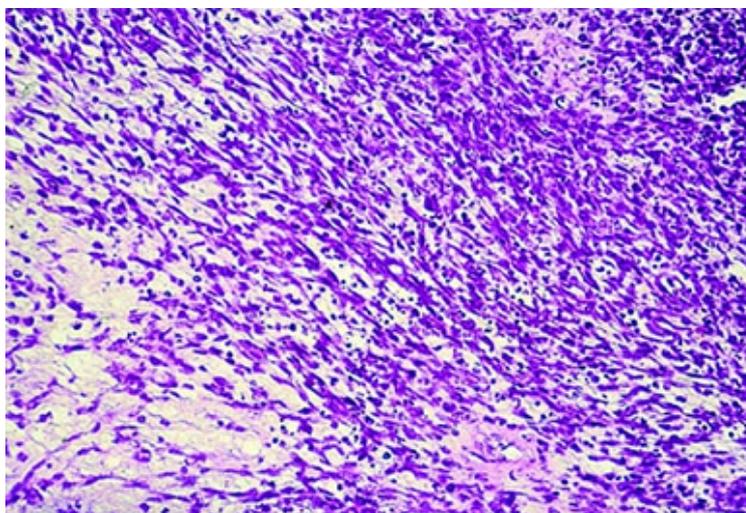
Clinics and pathology

Embryonic origin

In many cases, ERMS occurs in regions without abundant or in some cases, regions without any detectable skeletal muscle. Therefore, the relationship of ERMS to skeletal muscle is not clear. However, it is postulated that ERMS is derived from mesenchymal precursors of mesodermal origin.

Epidemiology

ERMS accounts for 70-80% of all RMS tumors, and usually occurs in young children (median age of 6.5 years). ERMS represents ~4% of all malignancies among children and adolescents, and has an annual incidence of ~4 per million.



Histopathology of ERMS (hematoxylin-eosin, original magnification: 100X; courtesy of Dr. Linda Ernst).

Clinics

ERMS often occurs in the head and neck region, genitourinary tract, and retroperitoneum. This tumor often presents as a painless mass, but in other cases, may be discovered from symptoms produced by compression of structures at the primary site. A small fraction of ERMS (10%) will have metastatic disease at the time of diagnosis, with the most frequent site of metastasis being the lungs. The standard treatment for ERMS is a combination of surgery, radiation, and intensive chemotherapy.

Pathology

The term embryonal RMS was coined to indicate the microscopic similarity of the tumor cells to developing skeletal myocytes. The tumor cells show variable myogenic differentiation, from small round cells to larger oblong cells with eosinophilic cytoplasm. In the most differentiated cells, there is a "strap-like" appearance, occasionally with cross striations and multinucleation. From an architectural standpoint, these tumors classically have variable cellularity, with hypercellular areas alternating with hypocellular areas containing a loose myxoid stroma.

Spindle cell RMS has dense whorls or bundles of spindle-shaped cells resembling smooth muscle. These tumors often occur in the paratesticular region of children and the head and neck region of adults. Botryoid RMS usually occurs in the lumen of a hollow internal organ, such as the urinary bladder or vagina. This form of RMS has the gross appearance of multiple polypoid nodules, and the microscopic appearance of a dense "cambium layer" of tumor cells under an intact epithelial surface.

Anaplasia is recognized by the presence of large, lobated hyperchromatic nuclei and atypical mitoses. Anaplastic cells can be found in a focal or diffuse distribution.

Prognosis

Patients with ERMS tumors have a better outcome than patients with ARMS tumors. The 4-year failure free survival rates for patients with localized and metastatic ARMS are 85% and 35%, respectively.

Other risk factors that influence outcome of ERMS include age, primary site, size of primary tumor, extent of local spread, and the presence of nodal and distal metastases. Based on these other factors, patients with ERMS tumors with limited extent of disease or in a favorable site (orbit, superficial head and neck, biliary tree, vagina, and paratestis) have a 85-95% probability of long-term survival. It should be also noted that though metastatic disease is a poor prognostic sign, patients with metastatic ERMS under 10 years of age have a survival rate of 40-50%, thus far exceeding the survival rate for metastatic ARMS.

Genetics

Though most cases of ERMS occur sporadically without an apparent genetic predisposition, a subset of ERMS occurs in association with the several genetic syndromes, including:

Neurofibromatosis type I (NF1)
Costello syndrome (HRAS)

Cytogenetics

Cytogenetics Morphological

In contrast to the recurrent chromosomal translocations found in ARMS, ERMS does not have recurrent structural chromosome rearrangements, but rather has frequent chromosome gains. The most notable gains in ERMS were chromosomes 2, 8, 11, 12, 13, and 20.

Comparative genomic hybridization studies indicated that usual ERMS tumors had a low frequency of amplification (6-10%) but anaplastic ERMS tumors had a higher frequency of amplification (67%).

Cytogenetics Molecular

There is frequently a loss of one of the two parental alleles at one or more contiguous chromosomal 11 loci in the tumor cells. The smallest chromosomal region of consistent allelic loss is 11p15.5. Multiple genes are present in this region and demonstrate expression that is epigenetically regulated in a parent-of-origin-specific fashion by genomic imprinting. It is postulated that one allele of a tumor suppressor gene in this region is physiologically inactivated by imprinting and the second allele is removed by the allelic loss event, and thus both alleles of the tumor suppressor are inactivated to promote an oncogenic effect.

Genes involved and proteins

IGF2

Location

11p15.5

Protein

Growth factor.

H19

Location

11p15.5

Protein

Non-coding RNA.

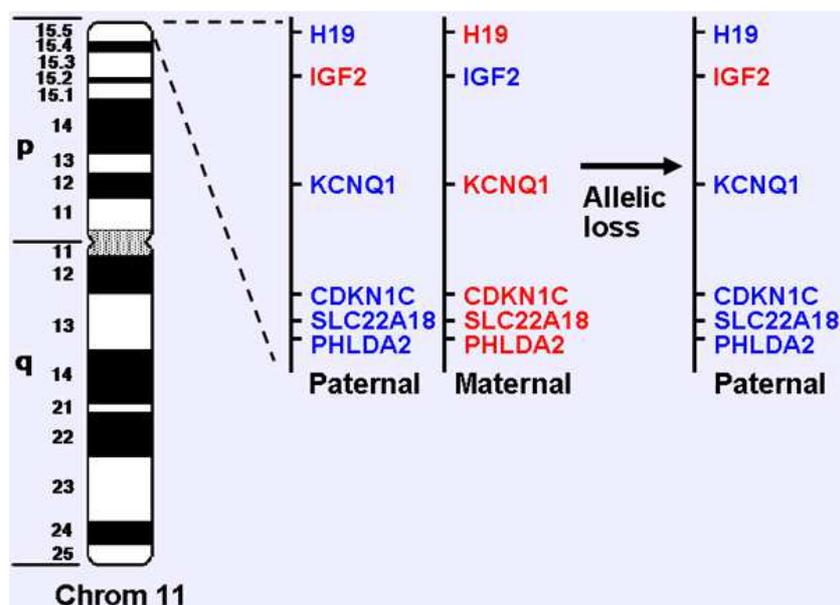
CDKN1C

Location

11p15.5

Protein

Kinase inhibitor.



Allelic loss of imprinted region at 11p15.5 in ERMS. In the 11p15.5 chromosomal region, there is parent-of-origin-specific expression (imprinting) of multiple genes, such that red indicates an expressed allele and blue indicates an unexpressed allele. In many cases of ERMS and other tumors, the maternal alleles in the 11p15.5 region (and variable amounts of contiguous regions) are lost by one of a variety of genomic mechanisms in a process termed allelic loss, loss of heterozygosity, or conversion to homozygosity.

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This article should be referenced as such:

Barr FG. Soft tissue tumors: Embryonal rhabdomyosarcoma. *Atlas Genet Cytogenet Oncol Haematol.* 2009; 13(12):986-988.