Embryonal Rhabdomyosarcoma

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Definition

Embryonal rhabdomyosarcoma (ERMS) is a malignant tumor deriving from embryonic skeletal muscle cells. It is also known as myosarcoma, malignant rhabdomyoma, rhabdopoietic sarcoma, rhabdosarcoma, embryonal sarcoma, botryoid rhabdomyosarcoma, and sarcoma botryoides.

Along with alveolar (ARMS), pleomorphic (PRMS), and spindle cell/sclerosing (SRMS) rhabdomyosarcoma (→ see dedicated sections), it belongs to the rhabdomyosarcoma family of tumors (for general details on these tumors → see section entitled "Rhabdomyosarcoma").

Epidemiology and Presentation

ERMS is the most common type of rhabdomyosarcoma and typically affects children aged less than 10 years (36% of all cases occur in children aged less than 5 years), with a slight male predominance. ERMS represents about 70% of childhood rhabdomyosarcoma cases and 20% of adulthood rhabdomyosarcoma cases.

Despite the name, fewer than 10% of ERMS cases develop within the skeletal muscles of the extremities. About 40% arise within the head and neck and 40% within the genitourinary system. Common sites include the urinary bladder, prostate, paratesticular soft tissues, periorbital soft tissues, oropharynx, parotid, auditory canal and middle ear, pterygoid fossa, nasopharynx, nasal passages and paranasal sinuses, tongue, and cheek. ERMS may also occur in the biliary tract, retroperitoneum, pelvis, perineum, as well as abdomen and viscera (e.g., the kidney and heart). The ERMS subtype called botryoid rhabdomyosarcoma is always confined to epithelial-lined viscera such as the urinary bladder, biliary tract, pharynx, conjunctiva, or auditory canal.

Clinically, ERMS causes symptoms related to the compression/infiltration of adjacent structures and organs, but it may simply present as a painless mass. Head

S. Mocellin, *Soft Tissue Tumors*, https://doi.org/10.1007/978-3-030-58710-9_81

and neck lesions may lead to proptosis, diplopia, sinusitis, or unilateral deafness; genitourinary lesions may cause a scrotal mass or urinary retention; biliary lesions may be associated with jaundice.

Etiology and Predisposition

Most ERMS cases are sporadic, but patients with some cancer predisposition syndromes are at higher risk of ERMS. For more details → see section entitled "Rhabdomyosarcoma" (paragraph "Predisposition").

Pathology

Macroscopically, ERMS presents as a poorly circumscribed, fleshy mass that impinges on adjacent structures; the botryoid subtype has a characteristic polypoid appearance (grape bunch appearance, hence the name) and abuts an epithelial surface.

Microscopically, ERMS (which resembles embryonic skeletal muscle) is composed of primitive mesenchymal cells in various stages of myogenesis, with a variable content of rhabdomyoblasts. Cell differentiation often becomes more evident after chemotherapy. Some tumors contain abundant, myxoid stroma (mimicking myxoma), while others comprise compact, patternless sheets of spindle and round cells. Especially in the case of a small biopsy, ERMS may only contain densely cellular sheets of round cells (rhabdomyosarcomas belong to the family of small blue round cell tumors → see also section entitled "Extraskeletal Ewing Sarcoma").

The botryoid variant (also known as sarcoma botryoides and botryoid embryonal rhabdomyosarcoma) contains linear aggregates of tumor cells (also known as the "cambium layer") that abut an epithelial surface.

Differential diagnosis may be needed with the following: alveolar rhabdomyosarcoma (strong nuclear staining for myogenin and MyoD1; molecular studies including FISH show PAX-FOXO1 fusion gene in approximately 80% of cases); desmoplastic small round cell tumor (tumor nodules on serosal surfaces, strongly positive for cytokeratin and EMA, it may be desmin positive but is MSA negative; it is associated with desmoplasia, and histologically it more closely mimics alveolar rather than embryonal rhabdomyosarcoma; it is negative for myogenin and MyoD1); Ewing/PNET (another small blue round cell tumor; it often displays Homer Wright rosettes, nuclei are far more uniform and pale, not dense and hyperchromatic; CD99 positive; desmin, MyoD1, and myogenin negative; it displays characteristic chromosomal rearrangements); lymphoma (positive for CD45, B-cell, or T-cell biomarkers; desmin, myogenin, MyoD1, and MSA negative); monophasic synovial sarcoma (negative for muscle biomarkers, usually far more spindled and organized in long fascicles; cytokeratin and EMA positive; it displays a typical chromosomal translocation); myxoid

liposarcoma (typically is easy to distinguish from ERMS, but it may have a very similar background matrix; signet ring lipoblasts; more bland histology and more uniformity when compared to ERMS; immunostaining and molecular features are also useful); neuroblastoma (undifferentiated neuroblastoma may be very difficult to distinguish histologically; elevated urinary catecholamines, rosettes, granular chromatin; S100, chromogranin, synaptophysin, and GFAP positive; lack of myogenic biomarkers); pleomorphic rhabdomyosarcoma (exclusively adults, usually deep soft tissue of the extremity and remarkable for its diffuse cytologic atypia; uniformly pleomorphic; it does not contain elements of embryonal rhabdomyosarcoma); and Wilms tumor (it may have rhabdomyoblastic differentiation, especially in the setting of chemotherapy; epithelial and blastemal components can be very focal following chemotherapy; WT1 and cytokeratin positive, muscle biomarkers negative).

Biomarkers

ERMS is typically positive for biomarkers of skeletal muscle differentiation, which correlate with the degree of tumor cell differentiation: in fact, only vimentin is present in the cytoplasm of the most primitive cells, while desmin and actin are acquired by developing rhabdomyoblasts, and only differentiated cells show biomarkers of terminal differentiation (e.g., creatine kinase M). MyoD and myogenin are highly specific and sensitive for rhabdomyosarcoma and are routinely used for diagnostic purposes (of note, only nuclear staining is specific, since nonspecific staining is common in paraffin-embedded tissues). Without myogenic differentiation (MyoD1 or myogenin) it is very difficult to diagnose ERMS; however, ERMS typically stains weakly/focally positive for myogenin, which is instead strongly positive for most cases of alveolar rhabdomyosarcoma.

Sporadic ERMS is cytogenetically aneuploid, with multiple numerical chromosome changes. Most cases share a loss of heterozygosity (LOH) localized to chromosomal region 11p15.5, which suggests the presence of a tumor suppressor gene inactivated during ERMS tumorigenesis by allelic loss of the active allele.

Syndromic ERMS implies different genes in the pathogenesis of this malignancy (→ see "Predisposition" paragraph of the section entitled "Rhabdomyosarcoma").

Prognosis

In general, ERMS has a better prognosis than the other types of rhabdomyosarcomas. Younger age is a favorable factor, while the outcome of parameningeal and extremity lesions is poorer than that of orbital and paratesticular lesions. Finally, botryoid rhabdomyosarcoma has a better prognosis as compared to standard ERMS.

For more details on staging and prognosis → see the section entitled "Rhabdomyosarcoma."

Therapy

Currently, risk-adapted multimodality treatment (personalized therapy) is the standard of care.

For details → see the section entitled "Rhabdomyosarcoma."

Suggested Readings

Fletcher (2020) WHO classification of tumours of soft tissue and bone, 5th edn

Garren (2020) NRAS associated RASopathy and embryonal rhabdomyosarcoma. Am J Med Genet A 182(1):195–200

McCluggage (2020) Embryonal rhabdomyosarcoma of the ovary and fallopian tube: rare neoplasms associated with germline and somatic DICER1 mutations. Am J Surg Pathol 44(6):738–747

Pappo (2018) Rhabdomyosarcoma, Ewing sarcoma, and other round cell sarcomas. J Clin Oncol 36(2):168–179

Skapek (2019) Rhabdomyosarcoma. Nat Rev Dis Primers 5(1):1

Tang (2018) The prognosis and effects of local treatment strategies for orbital embryonal rhabdomyosarcoma: a population-based study. Cancer Manag Res 10:1727–1734