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Rhabdomyoma and rhabdomyosarcoma

Embryonic rhabdomyogenesis is a highly conserved process that is replicated by both normal and neoplastic mesenchymal cells. Embryonal rhabdomyosarcomas in particular can show genetic and morphologic similarity to this process. Myogenesis begins at the early stage of the embryo, when the neural tube begins expression of PAX3. This in turn initiates the promoter region of MyoD1 and related proteins to begin expression of nuclear transcription factors, which in turn insert into the promoter regions of myogenic protein genes such as desmin, creatine kinase, and myosin. The end result of this process is of production of long filamentous proteins formed by cytoplasmic ribosomes and packaged into a complex filamentous structure capable of motility. At the light microscopic level, this process is recognized by the transformation of undifferentiated stellate mesenchymal cells into elongate cells with brightly eosinophilic cytoplasm. These rhabdomyoblasts fuse to form myotubes, which show progressive migrate of nuclei to the periphery and cytoplasmic elongation, forming mature myofibers.

Rhabdomyoma

Rhabdomyoma is a benign soft tissue counterpart of rhabdomyosarcoma. Unlike rhabdomyosarcoma, it is a rare lesion that comprises less than 2% of soft tissue neoplasms. Of these, most belong to the cardiac subtype, predominantly seen in tuberous sclerosis patients. Non-cardiac types have 3 major morphologies punctuation: fetal, adult, and genital.

Fetal rhabdomyomas usually occur in patients less than 3 years of age. These lesions are more common in boys, and they may occur as sporadic tumors or associated with basal cell nevus (Gorlin syndrome). They occur more commonly in the head and neck, particularly in the postauricular region. These lesions are much less common than rhabdomyosarcoma, but they resemble differentiated forms of that lesion. Rhabdomyosarcoma may also be associated with Gorlin's syndrome. Histologically, fetal rhabdomyoma forms parallel bundles of spindle cells and myoid cells, separated by less differentiated mesenchymal cells into a biphasic pattern. There should be no significant nuclear pleomorphism, low mitotic activity, and a well-defined capsule. Intermediate forms may resemble adult rhabdomyomas and contain both smooth and skeletal muscle. Of note, these lesions should be distinguished from spindle cell and embryonal rhabdomyosarcoma, but they should display no cambium layer, have a lower mitotic rate, show more circumscription, and occur in favored locations. Pretreatment material should be used for differential diagnosis, as post treatment rhabdomyosarcoma can show marked differentiation. By immunohistochemistry, rhabdomyomas express markers of differentiated muscle, such as myoglobin, desmin, and actin. They should be negative for cytokeratin and CD68. The latter marker may be strongly expressed by histiocytic lesions, which on occasion are desmin-positive. Genetically, fetal rhabdomyomas are characterized by mutations of the PTCH1 gene, this pathway may be activated in both sporadic and syndrome linked lesions.

Adult rhabdomyomas are rare benign neoplasms composed of mature, differentiated rhabdomyoblasts. These lesions typically occur in older adolescence and adults. On occasion, similar lesions may be seen in neural tumors. Like fetal rhabdomyoma, these lesions typically occur in the superficial soft tissues of the head and neck, particularly the oral cavity. Although the age is 50 years, rare pediatric cases may be seen. Up to 20% of these lesions are multifocal. Local recurrence may be seen, even years after excision. Differential diagnosis includes granular cell tumor, hibernoma, and crystal storing histiocytosis. Granular cell tumor is S100-positive and desmin-negative, similar to hibernoma. Crystal storing histiocytosis is CD68-positive and desmin-negative, and by electron microscopy it contains unique crystals.

Genital rhabdomyomas are benign myogenic tumors mainly occurring in the female genital tract. They appear to originate from mesenchymal stem cells within the subepithelial stroma. These usually occur in the vagina or cervix of reproductive aged women, and they may be pregnancy associated. This name has also been given to male genital lesions, but the latter look more like fetal rhabdomyomas. Female lesions resemble adult rhabdomyomas and should contain no significant pleomorphism, easily identifiable cross striations, and no significant mitotic activity. Beware of misdiagnosing “botryoid rhabdomyosarcoma” in reproductive age women, particularly in connection with pregnancy.

A variety of miscellaneous benign and tumors may contain muscle. These include neuromuscular choristoma, or benign triton tumor, which occurs as a hamartomatous lesion of peripheral nerve. These lesions form muscle within perineurial sheaths and mostly occur in the head and neck. EMA may be used to delineate perineurial sheets that enclose differentiating skeletal muscle. Rhabdomyomatous mesenchymal hamartoma also primarily occurs within the head and neck, usually the skin and mouth of newborn infants. These contain strands of skeletal muscle and myotubes with crossed striations. Focal myositis may form a solitary mass containing degenerating and regenerating skeletal muscle with infiltrates of lymphocytes and macrophages. These lesions have no clear association with polymyositis and may cause confusion with myogenic neoplasms.

Rhabdomyosarcoma

Rhabdomyosarcoma is the most common soft tissue sarcoma occurring in children. There are several varieties, including embryonal rhabdomyosarcoma, alveolar rhabdomyosarcoma, spindle cell rhabdomyosarcoma, and pleomorphic or adult rhabdomyosarcoma. Embryonal rhabdomyosarcoma predominantly occurs in young children, and it mimics embryonal rhabdomyogenesis both at the histologic and genetic level. Pleomorphic rhabdomyosarcoma on the other hand always occurs in adults and more resembles typical high-grade sarcomas occurring in that age range. Alveolar rhabdomyosarcoma is a separate category that response poorly to chemotherapy after recurrence and has unique genetic features that set it apart from the other categories. Spindle cell rhabdomyosarcoma occurs in both children and adults, and in the latter group it frequently shows unique mutations of the MyoD1 gene.

Most rhabdomyosarcoma is present as a painless mass. Rarely patients may have systemic problems such as hypercalcemia. Often symptoms relate to affected organs that have some degree of blockage or protrusion, causing features such as proptosis, visual field disorder, urinary retention, or jaundice.

Patient with rhabdomyosarcomas may be affected by various genetic syndromes, such as Li-Fraumeni, Beckwith Wiedemann, neurofibromatosis 1, Gorlin's syndrome, and pleuropulmonary blastoma syndrome. Although many describe rhabdomyosarcomas as tumors of skeletal muscle, many if not most tumors do not arise within the extremities. A more accurate description would be a tumor of primitive mesenchyme with a propensity to skeletal differentiation.

Histologically, rhabdomyosarcomas contain a mixture of rhabdomyoblasts and undifferentiated mesenchymal cells. Scattered multinucleated cells may be present, representing fused myoblasts. With therapy, differentiation into mature appearing skeletal muscle occurs.

Embryonal rhabdomyosarcomas have the features of embryonic muscle, with focal adhesive cell cells forming compact bundles and creating a "loose and dense" pattern within a loose myxoid stroma. Botryoid forms form polypoid masses within the vagina, urinary bladder, mouth, and bile ducts. These lesions typically occur in children less than 10 years of age and are otherwise extremely rare. Within pediatrics, embryonal tumors comprise the most common variety of rhabdomyosarcoma. Genetically, they show no specific single mutations, but they frequently exhibit a profound loss of heterozygosity on chromosome 11p, which is associated with imprinting abnormalities. Karyotypes often show a mixture of chromosomal deletions and duplications, with certain loci being preferentially affected. Differential diagnosis includes malignant peripheral nerve sheath tumor, which may contain embryonal rhabdomyosarcoma-like foci (the so-called malignant triton tumor). Myofibroblastic tumors, particularly inflammatory myofibroblastic tumor, may resemble rhabdomyosarcoma but should be negative for myogenin and MyoD1. Both rhabdomyosarcoma and myofibroblastic tumors may be ALK-positive. One should also avoid misdiagnosis of eosinophilic and inflammatory lesions within the urinary bladder, which can create polypoid masses resembling rhabdomyosarcoma.

Spindle cell and sclerosing rhabdomyosarcomas comprise a single recently recognized subtype in the World Health Organization Classification. These lesions contain bundles of spindle cells resembling fibrosarcoma and smooth muscle neoplasms. They may contain dense hyalinized collagen, which comprises the sclerosing variant. Pediatric examples show a predilection for the paratesticular region and also occur within the head and neck and extremities. Clinically, pediatric tumors have been characterized by having a relatively favorable prognosis, which differs from the relatively aggressive behavior shown by adult tumors. Spindle cell rhabdomyosarcomas by definition must contain at least 80% spindle cell histology, although some paratesticular tumors may show focal embryonal features. Lesions with smooth muscle features may be positive for smooth muscle actin, and isolated well differentiated cells may show cross striations. With sclerosing rhabdomyosarcoma, hyalinizing collagen entraps tumor cells and often appears osteoid-like or chondroid. These may have a small cell component causing confusion with alveolar rhabdomyosarcoma. Genetically, about one half of adult spindle cell rhabdomyosarcomas contain activating mutations in the MyoD1 gene, which is located on chromosome 11p. Infantile spindle cell rhabdomyosarcomas may have rearrangements of the NCOA2 gene, which on occasion may be seen as an alternate partner for PAX7 in tumors with alveolar histology. Differential diagnosis of these lesions includes leiomyosarcoma, fibrosarcoma, synovial sarcoma, spindle cell carcinoma, osteosarcoma, and some forms of angiosarcoma. Positivity for myogenin, MyoD1, and desmin help to separate them from the other tumors. Synovial sarcomas should be excluded by SS18 FISH.

Alveolar rhabdomyosarcomas are small cell neoplasms that may form patternless sheets of undifferentiated cells or a distinct alveolar pattern with floating clusters of cells and hanging single periseptal rows that have a picket row appearance. Many of these lesions show a t(1;13) or t(2;13) translocation, with fusion of FOXO1 to PAX3 or PAX7. Alveolar rhabdomyosarcomas often occur in the extremities, and some reports insinuate that they arise from differentiated muscle cells. They may also be seen within the sinonasal region and in the parameningeal region. They have a propensity to metastasize to regional lymph nodes. Although they tend to predominate in older children and adolescents, they may also occur in young children as well as adults. Incompletely excised lesions tend to recur and show drug resistance. Rarely, lesions may present as hematopoietic neoplasms, with leukemic involvement. Genetically, about 60% of cases with alveolar histology show a PAX3-FOXO1 fusion, which is overexpressed. About 20% of cases show a PAX7-FOXO1 fusion, which is typically amplified and forms double minutes seen on FISH. Some of these latter lesions may lack an apparent balanced translocation on routine karyotypes. The remainder of lesions with alveolar histology (about 20%) lacks an apparent fusion. Although these fusion-negative lesions have been considered to be high-grade tumors in the past, recent studies indicate that fusion-negative tumors are clinically and biologically more akin to embryonal rhabdomyosarcoma. Solid variant alveolar tumors in particular may be fusion-negative, and all of these lesions will require testing for entry onto future COG treatment protocols. Differential diagnosis of alveolar rhabdomyosarcomas includes the panoply of small round cell neoplasms, including Ewing's sarcoma, lymphoma, leukemia, neuroblastoma, and synovial sarcoma.

Pleomorphic rhabdomyosarcoma occurs as a high-grade sarcoma of the extremities and only occur in adults. By definition these lesion should have definitive evidence of skeletal myogenesis, which often requires immunohistochemistry with myogenic and desmin. These lesions usually occur in the lower extremities, but other sites may be affected, including orbit, chest wall, spermatic cord, abdomen, and arm. There is a wide age range, 21-81 years, with a medium of 54 years. These are aggressive lesions with 70% mortality and mean survival of 20 months. Microscopically, these lesions contain pleomorphic spindle cells and giant cells that may show a malignant fibrous histiocytoma-like pattern with storiform features. They contain cells with eosinophilic cytoplasm arranged in interwoven into a streaming or indistinct pattern. Although desmin can be helpful for diagnosis, it does not exclude smooth muscle tumors. Therefore, cytological evidence of skeletal myogenesis should be identified, as these lesions may be myogenin-negative. There are a few good studies of the genetic features of pleomorphic rhabdomyosarcomas, which typically show regions of chromosomal gain loss and genetic amplification, similar to osteosarcoma. Differential diagnosis includes undifferentiated pleomorphic sarcoma, dedifferentiated liposarcoma, dedifferentiated chondrosarcoma, melanoma, spindle cell carcinoma and carcinosarcoma.

The latter lesions have recently been used to define a new variant of rhabdomyosarcoma resembling epithelioid neoplasms: epithelioid rhabdomyosarcoma. A recent paper describes examples of this lesion in children, and they by definition should have features resembling epithelioid neoplasms. Many of these lesions contain rhabdoid cells, but they should show retention of INI1 gene expression by immunohistochemistry. Rhabdomyosarcomas containing rhabdoid cells have also been described in previous publications. In particular, one should beware of desmin-positive melanomas in the differential diagnosis. Epithelioid rhabdomyosarcomas are also fusion-negative and may show weak or focal myogenin expression.

A variety of myogenic markers have been used for immunohistochemical diagnosis of rhabdomyosarcoma. These markers of muscle differentiation include muscle actin, desmin, myoglobin, and myosin. Myogenic transcription factors, particularly MyoD1 and myogenin have become standard additions to immunohistochemical panels. These latter stains should show nuclear expression, as cytoplasmic expression is nonspecific. Myogenin shows a distinct pattern of diffuse strong expression with alveolar rhabdomyosarcomas and a weak or patchy expression pattern with embryonal rhabdomyosarcomas. It has been used in combination with surrogate markers of PAX-fusion to diagnosis alveolar rhabdomyosarcoma. PAX-fusion markers also include NOS-1, AP2beta, and P-cadherin. Conversely, HMGA2, EGFR, and fibrillin-2 appear to be expressed in fusion- negative tumors.

Assignment of a treatment group for rhabdomyosarcomas is a rather complex affair which must take site, age, lymph node metastasis, and distant metastasis into account. Staging is a clinical decision based on radiographic and clinical evidence of metastatic disease and the site of involvement. Certain sites have a relatively good outcome; these include orbit, paratesticular region, and female genital tract. Sites such as extremities and paravertebral region have a relatively poor outcome. Regardless of site, all lesions should be completely excised if possible. Surgical and pathologic evaluation defines tumor group, based on involvement of inked margins or gross evidence of extension outside of surgical boundaries. Histologic classification has traditionally affected failure-free and overall survival but appears to have largely been the effect of fusion positivity in the alveolar subtype. For this reason, genetics will be used rather than histology to define treatment groups on future COG trials.

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