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Rhabdomyosarcoma – A Recent Update

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Abstract

Rhabdomyosarcomas are aggressive soft tissue sarcomas that arise from primitive mesenchymal cells and often affect children and adolescents. this review provides an overview of their pathological features, diagnostic methods and treatment modalities, emphasizing the need for multimodal approaches that include surgery, chemotherapy and radiotherapy. despite the advances, challenges related to prognosis and metastatic potential underscore the importance of continued research to refine treatment strategies and improve outcomes for patients with rhabdomyosarcoma.

Keywords: Rhabdomyosarcoma, Alveolar, Botryoid, Pleomorphic, Embryonal

Introduction

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in children. It represents a high-grade neoplasm of skeletal myoblast-like cells. Soft tissue sarcoma accounts for ~7% of cancers in children and nearly 1% of cancers in adults[1]. rhabdomyosarcoma subtypes exist in two major types, 'alveolar' rhabdomyosacrcoma (ARMS) and 'embryonal' rhabdomyosarcoma (ERMS), which are driven by fundamentally different mechanisms.

It presents a fascinating array of histological aspects that feature the cytological stages of myogenesis and the interaction of neoplastic rhabdomyoblasts with the adjacent connective tissue matrix[2]. They arise at any anatomic site of the body; however, the extremities are the most common site in adults, followed by the trunk, genitourinary tract, head, and neck[3]. 2 Patients are assigned a risk group based on clinicopathologic features, which then determines treatment with bimodal therapy that may include chemotherapy, surgery, and/or radiation therapy[4].

Epidomology

Rhabdomyosarcoma is a common form of childhood cancer and is the most. The overall incidence rate of rhabdomyosarcoma is approximately 4 to 4.5 patients per million individuals aged less than 20 years. In the US, this equates to ~350 new cases per year[5]. On the basis of data from the Surveillance, Epidemiology and End Results (SEER) Program that the incidence of rhabdomyosarcoma differs both by age and Histology. The incidence of rhabdomyosarcoma in Europe appears to be similar to that in the US. The incidence of rhabdomyosarcoma appears to be lower in parts of Asia with just over 2 Patients per million individuals[6-7].

Influence of age and sex

Rhabdomyosarcoma incidence rates are determined by several factors intrinsic to the tumor and to individual patients. ERMS is the most common form in early childhood but some data suggests that it may also occur as second peak in early adolescence for

ERMS. Rate of ARMS occurance remains unchanged throughout childhood and adolescence[8]. WHO-classified pleomorphic rhabdomyosarcoma primarily occurs in adult males in their 60-70 years of age. Rhabdomyosarcoma incidence also varies by gender, as male children are more prone to ERMS Compared to female children (male : female ratio of 1.51) . Using data from SEER, the incidence of ERMS for the period of 1975–2005 to have remained stable. In contrast, a marked increase in the incidence of ARMS was evident over the same period[9-10].

Environmental factors

Many environmental exposures and other factors have been involved in rhabdomyosarcoma risk in children. Based on a study of people around less than 20 years of age with same culture have increased risk for rhabdomyosarcoma when exposed to prenatal X-ray, parental recreational drug use.

Classification

Horn-Enterline

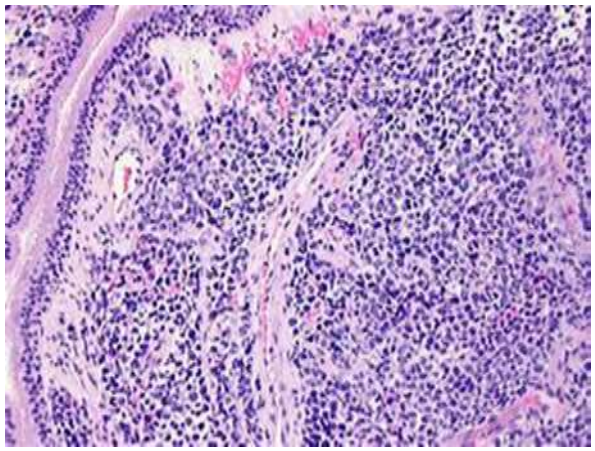
In 1958, Horn and Enterline proposed[11] that rhabdomyosarcomas could be subdivided into embryonal, alveolar, botryoid, and pleomorphic types.The cytoplasm was either dense or loose with myxoid matrix appearance.

Embryonal rhabdomyosarcomas(ERMS) is the most common subtype. ERMS arose in infants and children of age 2 to 8 years, in the head, neck and urogenital tract.

Clinical Features: Embryonic rhabdomyosarcoma, which often occurs in children, accounted for 60-70% of all rhabdomyosarcomas in that age group. These tumors can appear anywhere, but are most often found in the urogenital area or the head and neck. It has been pointed out that these tumors arise mainly from the musculature of the eye socket, face and cervix[18].

Histological Features: O'Day and colleagues described embryonal rhabdomyosarcoma as a mixture of four cell types:

Eosinophilic spindle cells, usually arranged in overlapping spiral chains. Round eosinophilic cells, large to medium-sized, with a small nucleus and granular eosinophilic cytoplasm, usually among other cell types. Broad, elongated eosinophilic cells with occasional cross-striations. Small round and spindle cells with darkly stained nuclei and little cytoplasm.



Alveolar rhabdomyosarcomas (ARMS) showed a unclear resemblance to fetal alveoli. ARMS is seen in adults mostly in parameningeal region.

Clinical Features: This subtype, which accounted for approximately twenty percent of all rhabdomyosarcomas in Enzinger and Shirak's analysis of more than 100 cases, has a much earlier onset, usually between 10 and 20 years, with a median age of 15 years. a year . However, the age group of that group was from 5 months to 58 years. The majority of cases of this type also occurred on the limbs, with approximately 18% observed in the head and neck region18.

Histological Features: Alveolar rhabdomyosarcoma is composed of relatively small, poorly differentiated, round and oval cells arranged in irregular clusters or nests separated by fibrous septa[18.]

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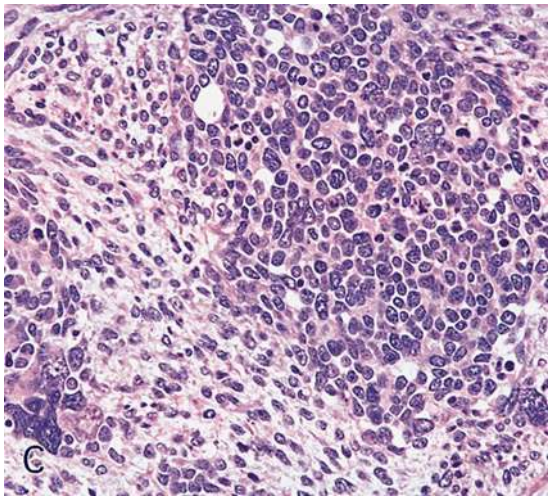
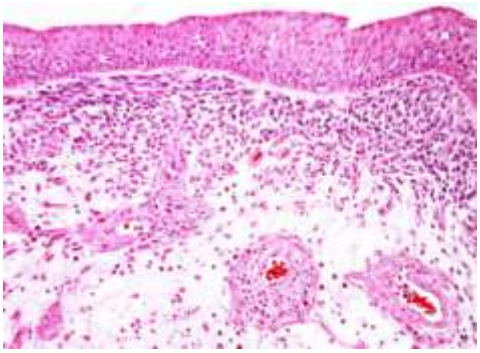


Botryoid rhabdomyosarcomas appears as grape-like polypoid masses partially lined by epithelium also known as “sarcoma botryoides”.

Clinical Features: It has been identified in young children as a malignant tumor of the vagina, prostate and bladder base. It is now widely recognized as a variant of embryonal rhabdomyosarcoma and has been reported to involve the sinus, nasopharynx, common bile duct and tympanic membrane. This tumor accounts for ten percent of all rhabdomyosarcoma cases18.

Histological Features:This subtype usually occurs under the mucosal surfaces of body openings; therefore, it is most often seen in places such as the vagina, bladder and nose. It is distinguished by the formation of polypoid and grape-like tumor masses. On histological examination, botryoid rhabdomyosarcoma shows malignant cells in a rich myxoid stroma.



Pleomorphic rhabdomyosarcoma(PRMS) most commonly occur in skeletal muscle of the extremities.

Clinical features: Pleomorphic rhabdomyosarcoma (the least common type) is a form of tumor that occurs more often in the limbs than elsewhere and is usually seen in older people. Depending on the location of the lesion, the following phenomena can be detected: eye abnormalities, speech disorders, difficulty in swallowing, cough, ear discharge or jaw deviation. Lesions are less often ulcerative and may invade the underlying bone and metastasize. The most common location for this condition is the head and neck area (35%)18.

Histological Features: Pleomorphic rhabdomyosarcoma consists mostly of randomly distributed spindle cells. These cells are usually large and vary considerably in appearance. Nuclei are ovoid or elongated and contain dense chromatin. A characteristic feature of this form of tumor is the presence of large own cells, the nuclei of which are often found at the elongated end of the cell, the "club" cell. "Belt" and "ribbon" cells usually have long cytoplasmic processes. Mitoses, especially

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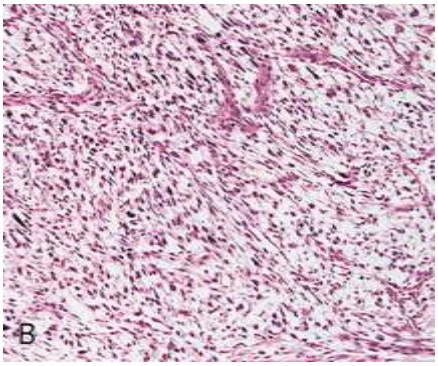
atypical ones, are common. The cytoplasm is eosinophilic and both intracellular longitudinal fibrils and transverse striations are seen. Cytoplasmic vacuoles also form as a result of the large amount of glycogen present in the cell. These tumors are undifferentiated, so identification of the cell of origin is impossible.



Palmer-IRSG

Palmer et al. introduced a completely new pattern for IRSG rhabdomyosarcomas, based on nuclear and cytological features instead of histology. Palmer et al. [12-14] recognized two cytological types, monomorphous round cell and anaplastic, with an unfavorable prognosis and another cytology, "spindle type A" with a superior prognosis. Tsokos et al [15] generated a new category, "solid variant" ARMS, which had the monomorphous round cell cytology of classical ARMS but lacked fibrous septa. Like the monomorphous round cell sarcoma of Palmer et al.'s classification, these tumors overlapped the survival curve of classical ARMS, which was an unfavourable outcome.

Immunohistochemistry

Immunohistochemistry can be used to distinguish ARMS from ERMS and also as a surrogate marker for fusion positivity. Dias et al. in 2000[19] showed that strong myogenin expression represented ARM causing diffuse immunostaining inconsistent with the variable, focal, heterogeneous pattern of ERMS. The strong expression of myogenin in ARMS is probably due to the downstream effects of PAX fusion proteins with regulatory elements of the myogenin gene [20]. However, there is considerable overlap in staining, and even botryoid tumors can show relatively strong expression in more than 50% of nuclei. On the other hand, fusion-positive ARMS tumors rarely show weak myogenin expression, and even the most differentiated ARMS tumors usually show expression in virtually all tumor cell nuclei. Gene expression analyzes revealed other proteins whose expression corresponds to the presence or absence of the PAX-FOXO1 fusion. Fusion-negative tumors preferentially express HMGA2, EGFR, and fibrillin-2, whereas fusion-positive tumors preferentially express TFAP2β and P-cadherin [21,22].

Molecular Diagnostics

The advent of molecular diagnostic tools has greatly contributed to the detection of rhabdomyosarcoma. Specifically, ARMS is more accurately diagnosed as FP rhabdomyosarcoma based on the detection of the presence of the PAX-FOXO1 fusion in tumor cells by FISH or detection of the fusion transcript by RT-PCR analyzes[23,24]. Systematic application of molecular diagnostic tests on biopsy specimens from pathologically diagnosed ARMS patients show that about 20% of these patients are negative for fusion transcript[25]. This finding is particularly important because the molecular characteristics and clinical outcomes of FN ARMS are similar to those of ERMS

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Children with FN ARMS are similar to children with ERMS[26,27]. Molecular diagnosis based on fusion status clears up some of the confusing questions about the usual pathology of rhabdomyosarcoma.

Molecular Factor

Almost 80% of tumors that are morphologically ARMS have FOXO1 fusion, while more than 95% of tumors that are morphologically ERMS do not have

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FOXO1 fusion 16 and we now understand that the presence or absence of the FOXO1 fusion gene causes rhabdomyosarcoma. Recent molecular diagnostics have discovered features in addition to FOXO1 fusion status that describe new molecular biomarkers not yet included in rhabdomyosarcoma risk stratification.

Diagnosis

Clinical Presentation

The diagnosis of rhabdomyosarcoma has traditionally been based on the identification of satellite cell characteristics, such as tumor cells, using light and, in some cases, electron microscopy and Immunohistochemical (IHC) staining for skeletal muscle proteins[28,29]. The most common sites of rhabdomyosarcoma depend on the histological subtype: ERMS occurs most often in the head and neck, including the orbit, or in urogenital sites; Hands are usually born at points on the limbs and a smaller part on the head and/or neck or body[30]. Metastases occur via both lymphatic and hematogenous routes and spread to the lungs, bones and bone marrow are very common[31].

Pathological Assessment

The diagnosis of rhabdomyosarcoma requires direct analysis of tumor tissue, either by surgical or excisional biopsy or needle biopsy, and is subjected to a series of histological and molecular pathological examinations. WHO recognized three histological variants of rhabdomyosarcoma – Alveolar rhabdomyosarcomas, pleomorphic rhabdomyosarcoma and Embryonal rhabdomyosarcoma – and ARMS and ERMS were the most common childhood rhabdomyosarcomas. A recent WHO update now includes spindle cell/sclerosing rhabdomyosarcoma as a separate entity[32].

Arms And Erms

Alveolar rhabdomyosarcomas and Embryonal rhabdomyosarcoma can be further subdivided by histological or molecular features. ARMS typically consists of tightly packed small round cells lining alveolar septa, while ERMS consists of immature rhabdomyoblasts in a less dense, stroma-rich background without an alveolar pattern[33].

Treatments

Treatment of locally advanced rhabdomyosarcoma is based mainly on surgery[34,35] although aggressive surgery, which is often necessary to remove the tumor and achieve negative microscopic margins, is no longer recommended[36]. This is especially true for genital rhabdomyosarcoma to prevent significant chronic conditions such as urinary tract infections, infertility and especially sexual dysfunction.

In support of delayed surgery, it has been shown that although rhabdomyosarcoma can occur even after neoadjuvant therapy[37,38], the number of rhabdomyoblasts found in subsequent biopsies gradually decreases and their presence does not indicate local recurrence[39,40].

Conclusion

In conclusion, rhabdomyosarcoma remains a major challenge in pediatric oncology. This aggressive soft tissue cancer affecting children and young adults warrants continued research and clinical efforts. Advances have been made in understanding its subtypes, improving diagnostic tools, and improving treatments. However, early detection and targeted therapies remain urgent areas. A collaborative, multidisciplinary approach is critical to optimizing patient outcomes. As the genetic background of rhabdomyosarcoma is deepened, the possibilities for personalized treatment continue to grow. Raising awareness, supporting research and improving access to healthcare are important steps towards a better prognosis and a better quality of life for people suffering from the disease.

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