Rhabdoid Tumor

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Definition

Rhabdoid tumor is a malignant neoplasm first described as a rhabdoid variant of Wilms tumor in the kidney. Although the term rhabdoid is derived from the histologic resemblance of tumor cells to rhabdomyoblasts, the cell of origin is still undefined. Rhabdoid tumor is characterized by loss of expression of SMARC proteins (→ see also Chap. 229).

It is also known as atypical teratoid rhabdoid tumor (ATRT, when localized in the central nervous system), rhabdoid tumor of the kidney (RTK), extra-central nervous system rhabdoid tumor, extracranial extrarenal rhabdoid tumor, and malignant rhabdoid tumor (MRT). Extracranial extrarenal rhabdoid tumor is also known as rhabdoid tumor of soft tissue (→ see Chap. 89).

Epidemiology and Presentation

Rhabdoid tumor is a rare malignancy occurring mainly in infants and children younger than age 3 years (although adult cases have been reported). The age-standardized annual incidence rate is between 5 (extracranial rhabdoid tumors) and 8 per million (atypical teratoid/rhabdoid tumor) in children younger than age 1 year and decreases to between 0.6 and 2.2 per million at ages 1–4 years. Rhabdoid tumor can arise in almost any anatomic location: commonly in the central nervous system (ATRT, more than 50% in the cerebellum) but also in the kidney (RTK) and in extracranial extrarenal sites (e.g., head and neck, paravertebral muscles, liver, bladder, mediastinum, retroperitoneum, pelvis, and heart).

Clinical presentation is dominated by the signs and symptoms related to the tumor mass effect on adjacent structures. The tumor may occur as a single disease or as a multifocal disease (synchronous or metachronous): distinguishing primary multifocal disease in the setting of SMARCB1 germline mutations from oligometastatic disease is basically arbitrary or impossible.

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Etiology and Predisposition

Rhabdoid tumor can develop as sporadic neoplasms but also within the frame of a hereditary condition known as **rhabdoid tumor predisposition syndrome** (RTPS). In both cases, biallelic inactivation of tumor suppressor gene SMARCB1[1] (most frequently) or SMARCA4[2] (sometimes) is typically found in tumor cells. Individuals with RTPS typically present before age 12 months with synchronous tumors that exhibit aggressive clinical behavior. RTPS predisposes also to the development of small cell carcinoma of the ovary hypercalcemic type (SCCOHT), an entity related to rhabdoid tumors and characterized by loss of SMARCA4 (not SMARCB1) expression. The diagnosis of RTPS is established in a proband with a rhabdoid tumor and/or a family history of rhabdoid tumor and/or multiple SMARCA4- or SMARCB1-deficient tumors (synchronous or metachronous) and identification of a germline heterozygous pathogenic variant in SMARCA4 or SMARCB1 by molecular genetic testing. Among newly diagnosed individuals with a rhabdoid tumor, 25–35% have a germline pathogenic variant in SMARCB1. RTPS is inherited in an autosomal dominant manner: the vast majority of individuals diagnosed with RTPS have the disorder as the result of a de novo germline SMARCB1 pathogenic variant. Most individuals diagnosed with RTPS inherited a pathogenic variant from an unaffected parent. Each child of an individual with a germline SMARCA4 or SMARCB1 pathogenic variant has a 50% chance of inheriting the pathogenic variant. However, penetrance appears to be incomplete, and the types of RTPS-related tumors can vary among different members of the same family. Prenatal diagnosis for pregnancies at increased risk is possible if the pathogenic variant in the family is known.

Individuals diagnosed with RTPS should be carefully followed up for secondary prevention purposes (i.e., tumor surveillance programs are necessary for early diagnosis of neoplasms).

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[1] SMARCB1: SWI/SNF-related matrix-associated actin-dependent regulator of chromatin, subfamily B, member 1 (also known as INI1) encodes a protein which is part of the BAF (hSWI/SNF) complex that relieves repressive chromatin structures, allowing the transcriptional machinery to access its targets more effectively. This ATP-dependent chromatin-remodeling complex plays an important role in different cell activities including cell differentiation; in particular, regulation of the stem cell-associated program, which is maintained by the repressive effect of the EZH2-dependent PRC2 (polycomb repressive complex 2), is disrupted by SMARCB1. Overall, SMARCB1 has been found to act as a tumor suppressor, and its mutations have been associated with a variety of malignancies including sarcomas.

[2] SMARCA4, located at 19p13, encodes the protein BRG1 and is part of the switch/sucrose-nonfermenting (SWI/SNF) chromatin remodeling complex that is also known as the BAF (BRG1-associated factors) complex. This complex is ATP-dependent and plays an important role in transcription, differentiation, and DNA repair and has been shown to behave as a tumor-suppressing complex. Each complex contains multiple subunits, each of which contains a mutually exclusive ATPase subunit, SMARCA4 (BRG1), or SMARCA2 (BRM).

Pathology

Microscopically, rhabdoid tumor usually presents as solid sheets of large cells with deep eosinophilic cytoplasm, possible laterally displaced nucleus, prominent nucleoli (rhabdoid cells, hence the name). Myxoid, hyalinized, pseudoalveolar areas may be present. Some cases display large anaplastic cells with similar nuclear morphology but frequently with more conspicuous macronucleoli; other less common patterns include small round cell and spindled morphologies that may represent focal findings in an otherwise conventional appearance or predominate, which represents a diagnostic challenge.

As morphologic rhabdoid features may not be present in all rhabdoid tumor biopsies because of inter- and intratumoral heterogeneity, any small blue round cell tumor in infants and young children should be evaluated for absence of nuclear SMARCB1/SMARCA4 staining.

Distinguishing rhabdoid tumor of soft tissue from proximal-type (large cell) epithelioid sarcoma on morphologic grounds alone is rather arbitrary as the extent of the rhabdoid differentiation might be the only feature that helps their distinction.

The theory of pure extrarenal rhabdoid tumors as a single nosological entity has been challenged by the observation of similarly rhabdoid cells as a component in otherwise differentiated neoplasms occurring at a wider age range, leading to the concept of composite extrarenal rhabdoid tumors as a common final pathway of dedifferentiation in a variety of neoplasms; recent studies from different organs confirmed the occurrence of true composite neoplasms composed of a differentiated (organ-specific, SWI/SNF intact) and an SWI/SNF-deficient undifferentiated variably rhabdoid component driven by secondary SWI/SNF gene deletions/inactivation.

Biomarkers

Immunohistochemically rhabdoid tumor cells may express vimentin, EMA, and cytokeratins. However, rhabdoid tumors are characterized by biallelic loss of SMARCB1 (see Footnote 1) or SMARCA4 (see Footnote 2): this feature can be demonstrated both at immunohistochemistry (absence of SMARCB1 or SMARCA4 expression) and at the molecular level (presence of somatic inactivating gene mutations). In subjects with RTPS, heterozygous loss of one of these genes can be found at the germline level (e.g., in the peripheral blood mononucleated cells).

Prognosis

Rhabdoid tumor is a highly aggressive neoplasm featuring early metastases (generally to lung, liver, and lymph nodes) and poor responsiveness to therapy. It is usually fatal within 1–2 years.

Therapy

Due to the rarity and recent identification of this nosological entity, standards for management are evolving. Most patients are treated by intensive multimodal therapeutic strategies combining surgery, radiotherapy, and chemotherapy. High-dose chemotherapy (with peripheral blood stem cell rescue) combined with radiotherapy has been recently reported to provide promising results.

Theoretically, SDTS might benefit from target therapy with inhibitors of enhancer of zeste homolog (EZH2) due to their activity against tumors with abnormalities in the SWI/SNF complex proteins: of note, one such drug called tazemetostat has been recently approved by the Food and Drug Administration for the treatment of epithelioid sarcoma (→ see dedicated section), a SMARCB1 deficient tumor.

As RTPS predisposes to the development of SCCOHT, prophylactic bilateral oophorectomy may be discussed after childbearing.

Suggested Readings

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