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Pediatric Malignancies and IHC

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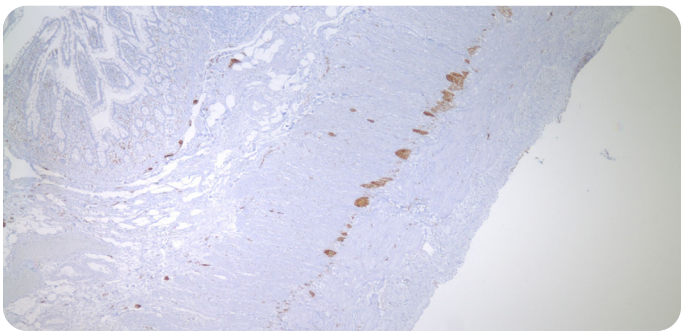
Pediatric tumors are heterogenous and can be quite varied in appearance. However, those in the infamous “small round blue-cell tumor” group, with their hyperchromatic nuclei and small amount of cytoplasm can be challenging, and their detection require cost-efficient and focused immunohistochemistry and ancillary testing. Ideally, ample material should be obtained for routine histology and ancillary testing, including immunohistochemistry, fluorescent *in situ* hybridization, fresh tissue for cytogenetic studies, and snap-frozen tumor for DNA/RNA extraction both for routine molecular testing (i.e., reverse-transcription PCR studies), as well as future research study protocols (genome wide studies, targeted gene sequencing). The term “blastoma” refers to a tumor that recapitulates its embryological origin. Although the cellular origin of many pediatric tumors is presumed and even accepted in many cases, it is important to emphasize that they are labeled according to their morphologic differentiation patterns.

Neuroblastoma

Neuroblastic tumors (NT) represent a spectrum with variable degrees of cell maturation along the embryological development of the sympathetic nervous system and include 3 main categories: neuroblastoma (NB), ganglioneuroblastoma (GNB), and ganglioneuroma (GN), based on the amount of S-100 positive schwannian stroma (SCHNS) and ganglion cell differentiation. The GN and GNB show abundant SCHNS. However, in GN, only mature ganglion cells are seen, frequently arranged in clusters surrounded only by SCHNS. In contrast, GNB shows ganglion cells and neuroblasts, with >50% of its tumor population undergoing synchronous ganglion cell differentiation, associated with fibrillary matrix (neuropil) in the background of abundant SCHNS. NBs, at the most immature end of the NT spectrum, are SCHNS-poor tumors composed of neuroblasts that range from small- size to medium-size cells, with round to slightly oval nuclei, “salt and pepper” chromatin, and inconspicuous nucleoli, depending on their degree of differentiation.

NBs usually are seen in young children; over 80% are detected in those under the age of 4 years, and the median age at diagnosis is 21 months. There is no sex predilection, NBs can exhibit familial incidence; be associated with Beckwith-Weidemann syndrome, Hirschsprung disease, and other congenital abnormalities; present in neurofibromatosis; or occur as a complication of fetal hydantoin syndrome. The usual presentation is in the form of an abdominal mass. About 70% of NBs occur in the retroperitoneum, and the majority involve the adrenal gland.[1]

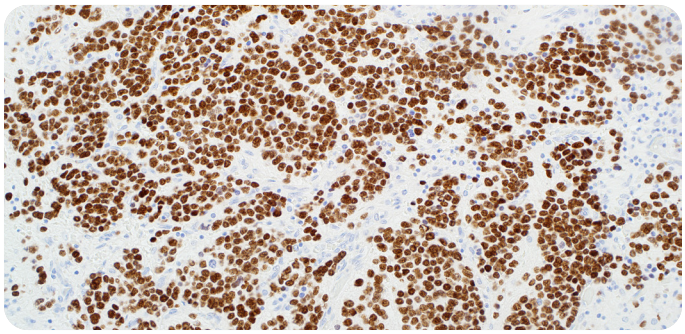


PGP 9.5

The Children’s Oncology Group’s NB Risk-Stratification System uses clinical and biological factors to predict behavior and outcomes. Immunohistochemistry can aid in highlighting the SCHNS which displays reactivity for S-100 protein, whereas maturing ganglion cells and neuroblastic cells are reactive for neural-specific markers including neuron-specific enolase (NSE), protein gene product 9.5 (PGP 9.5), synaptophysin, NB84 (antibody to NB cell lines), CD56, CD57, and tyrosine hydroxylase.

Similar to CD99, PGP 9.5 may show cytoplasmic staining within a number of other tumors with neuroectodermal lineage, including Ewing sarcoma family of tumors (EWSFT), synovial sarcoma (SS), malignant peripheral nerve sheath tumor (MPNST), neurofibroma, and even two cases of rhabdomyosarcoma (RMS).[2]

By contrast, CD99 and Friend leukemia virus integration 1 (FLI-1) are typically negative in NB and help rule out a neoplasm of the EWSFT. In addition, lymphoid and myogenic markers should also be employed when neuropil and/or scant SCHNS are difficult to assess, as in small biopsy samples of poorly or undifferentiated NB. NTs generally lack reactivity for vimentin, smooth muscle actin (SMA), desmin, cytokeratin, and CD45. Up to 40% of aggressive NBs (predominantly undifferentiated and poorly differentiated subtypes) demonstrate MYCN amplification.

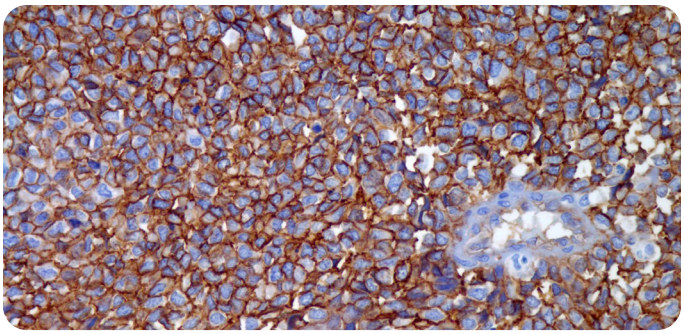


PHOX2B

The gene PHOX2B, which encodes a transcription factor highly specific for the autonomic nervous system, is mutated in familial and syndromic peripheral NT and recently has been suggested by Bielle et al[7] as a sensitive and specific marker of peripheral NT. Although nuclear expression is also present in other neoplastic and normal tissue derived from the autonomic nervous system (i.e., paragangliomas, neurons, chromaffin cells), no expression was found in 79 other pediatric “small round blue-cell” tumors. The caveat of this study is that while an extensive group of varied pediatric tumors was stained with the PHOX2B antibody, each group contained only a few cases, thus only time and experience will truly test its value.[3]

Ewing Sarcoma Family Of Tumors

EWSFT includes Ewing sarcoma (ES: osseous and extraosseous), peripheral Primitive Neuroectodermal Tumor (pPNET), and Askin tumor (a pPNET of the chest wall). This family of tumors was one of the first groups of pediatric tumors to be defined by a signature translocation.[4-6] The classic histologic features include a monomorphic population of densely packed sheets of generally small and "round blue" cells with scant cytoplasm, with alternating "light" and "dark" cells, imparted by the open nuclei of light cells displaying evenly dispersed chromatin, whereas darker cells have slight nuclear contour irregularities with clumped chromatin. Partial neural differentiation represented by Homer-Wright or Flexner-Wintersteiner rosettes may also be present.



CD99

Atypical examples of the EWSFT display larger nuclei with prominent nucleoli and may contain more stroma imparting a nodular appearance, which is best highlighted by a reticulin stain. The EWSFT classically show a strong and diffuse membranous expression of CD99 (MIC2), a membrane glycoprotein encoded on both the X and Y chromosomes (i.e., a "pseudoautosomal" gene), which plays a role in apoptosis, cell migration, and adhesion.[7-9]

Membranous CD99 staining (initially described in lymphocytes) is highly sensitive but not specific for EWSFT (as it can be expressed in other round blue-cell tumors including lymphoblastic lymphomas, SS, desmoplastic small round cell tumor (DSRCT), malignant rhabdoid tumor (MRT), and even rare cases of RMS in either a membranous or cytoplasmic dot-like pattern.[10-15] Therefore, it is recommended to always include a lymphoid marker such as CD45 (LCA) or CD43 and TdT, as in children some cases of lymphoblastic lymphoma may be CD45- making screening with TdT imperative. Also, an epithelial marker such as epithelial membrane antigen (EMA) and cytokeratin AE1 & AE3 should be used in the initial antibody panel approach.

However, about 20% to 30% of cases with typical EWSFT histology may express low–molecular-weight keratins (ie, CAM 5.2) and/or pancytokeratin (AE1 & AE3) in either a diffuse membranous/cytoplasmic or focal perinuclear dot-like to pattern.[16,17] Furthermore, many of the cases with atypical morphology (ie, large cell, spindle cell, sclerosing variants) also express cytokeratin, including the adamantinoma-like variants which also express high–molecular-weight keratins (HMWCK) 1, 5, 10, and 14/15.[13,17] EWSFT also can also show nuclear expression of FLI-1, a member of the erythroblastosis virus-associated transforming sequence family of DNA-binding transcription factors. In cases with known ES gene rearrangement, the sensitivity of FLI-1 with polyclonal sera is about 91%,[17-19] FLI-1 also has a wide expression noted in vascular tumors (ie, epithelioid angiosarcoma), Merkle cell carcinoma (CD99+/ FLI-1+/CK 20+), malignant melanoma (FLI-1+/S-100+/Melan A+), along with other small round cell CD99- positive mimics including lymphoblastic lymphoma, SS. FLI-1 expression has not been reported in RMS, NB, Wilms tumor (WT), and mesenchymal chondrosarcoma, and normal expression is seen in native tissue mostly limited to endothelial and hematopoietic cells.[20,21] Thus, as with any marker, FLI-1 should be used with a panel, knowing its range of tumor expression.

Desmoplastic Small Round Cell Tumor

Desmoplastic small round cell tumor (DSRCT), usually a tumor of young adults, is rarely seen in young children and has a predilection for intra-abdominal sites. Having been described in the pleura, it also occurs in the kidneys and other viscera, but is frequently in the differential diagnosis of EWSFT. Although a subset of DSRCT cases may have CD99 immunoreactivity, they typically lack the crisp membranous expression characteristic of EWSFT. However, the shared histologic and immunophenotypic overlap with EWSFT is further confounded when desmoplastic stromal representation is lacking (i.e., small biopsy samples) and when only using the EWSR1 FISH break-apart probe which will be positive. In those instances, DSRCT may be confirmed based on its divergent differentiation, with staining for mesenchymal markers (vimentin and desmin with its typical paranuclear dot-like pattern or less often diffuse cytoplasmic pattern), epithelial markers (AE1 & AE3, EMA, CAM 5.2), neural markers (synaptophysin and NSE), and strong nuclear WT1 expression, which further differentiates it from EWSFT.

Furthermore, the EWSR1/WT1 fusion should be confirmed by FISH, RT-PCR, and the classic cytogenetic karyotype t(11;22)(p13;q11), especially in cases when histology and immunophenotyping are not straightforward.[10]

Rhabdomyosarcoma

Rhabdomyosarcoma (RMS) is the most prevalent soft-tissue sarcoma of the pediatric population. Two of the 3 major subtypes predominate in childhood: embryonal (ERMS) and alveolar (ARMS), whereas the pleomorphic variant is more frequently diagnosed in the adult population. RMS is thought to derive from a primitive mesenchymal cell of skeletal muscle lineage, having a variable amount of differentiating rhabdomyoblasts present in the tumor. The ERMS is more frequently seen in the head and neck, abdomen, and genitourinary

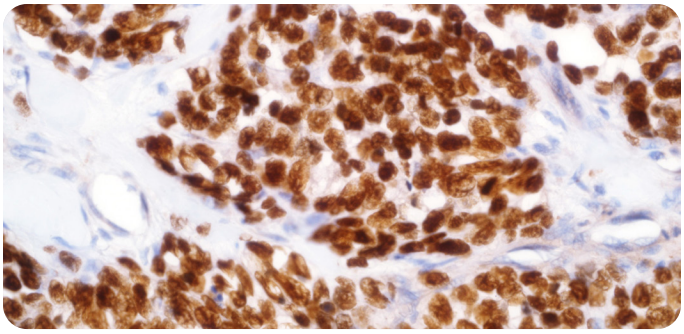
sites, whereas the ARMS is more frequently found within the soft tissues of the extremities and within parameningeal and paranasal sinuses, but can occur at any site in the body. The International Classification of RMS, which is included in the WHO classification[22] recognizes ERMS as displaying a more primitive mesenchymal appearance with a myxoid background. When ERMS occurs in a hollow viscus like the urinary bladder, it may adopt the pattern called "botryoid" subtype, forming grape-like or vaguely papillary clusters with a condensed neoplastic subepithelial cellular cambium layer. Other subtypes under the ERMS heading include the spindle cell and sclerosing variants.

The spindle-cell subtype is found predominantly in paratesticular and orbital soft-tissue regions, has a whorled, storiform pattern with scattered, large, atypical cells but no true "anaplasia" (ie, 3-fold nuclear enlargement and/or atypical mitoses).[22,23] In contrast, the sclerosing variant features significant fibrous elements separating neoplastic cells, which may impart a scirrhous carcinoma-like pattern causing confusion with chondrosarcoma, osteosarcoma, or even angiosarcoma if myogenic markers are not utilized.[24] Furthermore, Jo et al[25] have recently described a morphologic variant called "epithelioid rhabdomyosarcoma" with histologic and clinical parameters similar to those of poorly differentiated carcinoma or melanoma, featuring sheets of epithelioid cells with large vesicular nuclei, prominent nucleoli, increased mitoses, necrosis, and infiltrative morphology, occurring more frequently in the adult population with a median age of 70.5 years (range, 14 to 78 years). The ARMS is a distinct subtype with characteristic spaces reminiscent of pulmonary alveoli formed by delicate septa to which the neoplastic cells are attached; frequently, these cells "float" as cellular nests within them.

While a "solid-alveolar" variant may closely resemble lymphoma or EWSFT due to its compact and poorly differentiated microscopic appearance, the key histologic landmark of RMS is evidence of rhabdomyoblastic differentiation, including ample eosinophilic cytoplasm and an eccentric large nucleus. The once gold standard ultrastructural analysis to demonstrate myogenesis with thick and thin filaments has been replaced by immunohistochemical demonstration of rhabdomyoblastic differentiation, with cytoplasmic staining of desmin and muscle specific actin, and the exclusive nuclear expression of the early myogenic transcription markers myogenin and myogenic regulatory protein (MyoD1).

MyoD1 and myogenin nuclear expression can be seen in other spindle and round cell neoplasms with small foci of primitive skeletal muscle differentiations (ie, rhabdomyomatous WT). Rare cases of RMS have been reported to show positivity to CD99 in a membranous to cytoplasmic paranuclear dot-like pattern[15] and cytoplasmic PGP 9.5.[2] The MyoD1 antibody often displays a high background of nonspecific cytoplasmic staining diminishing its utility; although some report that sclerosing RMS subtype have stronger MyoD1 expression as compared with relatively weaker myogenin expression.[26]

Rhabdomyosarcoma is the most prevalent soft-tissue sarcoma of the pediatric population.



MyoD1

It should be noted that myogenin often has more focal nuclear staining in ERMS, in comparison with the diffuse nuclear staining in ARMS[27] and should always be used in conjunction with desmin.

The molecular characterization of fusion-positive ARMS is still the most important ancillary test in distinguishing between the different types of RMS. The ARMS is characterized by the fusion of the DNA-binding domain of the paired box PAX genes, PAX-3 at 2q35 or PAX-7 at 1p36, to the transcriptional activation domain of the forkhead homolog 1 rhabdomyosarcoma transcription factor (FOX01A/FKHR) at 13q14. The chimeric PAX-3/FKHRmRNA transcript produces an oncogenic protein responsible for inducing a skeletal muscle genetic expression program through transcription factors such as myogenin, MyoD1, SIX1, and SLUG.[28]

Synovial Sarcoma

Synovial sarcoma (SS) is a rare tumor with predilection for the periarticular connective spaces of the distal lower extremity around the knee, followed by the upper extremity. However, SS is not limited to the joints and can be found in axial locations in 25% of cases (head-neck, trunk, lung, pleura, and retroperitoneum).[29,30] There are two major histologic subtypes: a classic biphasic pattern combining epithelioid glandular elements with uniformly spindle cells, showing pale nuclei, finely granular chromatin, rare to absent mitotic figures, and inconspicuous cytoplasm; and a second, more common monophasic pattern, with a more spindled phenotype showing alternating light and dark areas imparted by variable hypocellular to hypercellular density, often mimicking a malignant peripheral nerve sheath tumor (MPNST). Rarely, a poorly differentiated subtype of the calcifying/ossifying and myxoid subtypes can be seen; however, these patterns are more commonly seen as foci within a monophasic or biphasic tumor.[31] Immunohistochemical stains are diffusely positive for vimentin and typically also for EMA in the spindled component, whereas cytokeratins (CK), especially CK 7 and CK 19, highlight the epithelioid cells but may be only focally positive in the spindle cells. In addition, cytoplasmic to membranous CD99 and cytoplasmic BCL2 are positive in SS. Not infrequently, a subset of SS will express S-100, leading to additional confusion with MPNST, which can have variable loss of staining, especially in high-grade MPNST.[32] There may be focal staining with calponin, SMA, and/or muscle specific actin, but desmin and h-caldesmon are typically negative.[33] In addition, there are reports of SS with loss of INI-1 nuclear expression[34,35] (typically seen in rhabdoid tumor) and a small percentage with nuclear β-catenin expression (characteristic of fibromatosis).[29]

A recent nuclear marker overexpressed in SS is TLE1, a competitor with β-catenin that causes repression of the Wnt signaling pathway via transcriptional repression of downstream targets.[36] TLE1 is expressed in both components of SS and appears to be a sensitive but not completely specific marker, as it is positive in a small fraction of solitary fibrous tumor/hemangiopericytomas (30%) and schwannomas (30%) with rare staining in MPNST (4.5%)[36]; however, others have shown a fairly specific staining profile when compared with other high-grade sarcomas.[37]

The MUC-4 immunostain, which has been shown to be a sensitive marker for low-grade fibromyxoid sarcoma, has also been reported to have strong but focal cytoplasmic staining of spindle cells in a subset of SSs.[38] The diagnostic translocation t(X;18)(p11.2:q11.2) is seen in at least 90% of cases and has aided in the correct classification of these spindle cell sarcomas.

Alveolar Soft Part Sarcoma

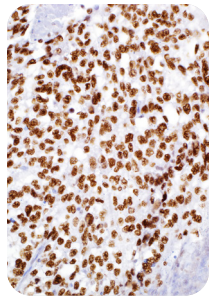
Alveolar soft part sarcoma (ASPS) is a rare tumor of uncertain lineage with variable location depending on the age of the patient. In adolescents and young adults, it predominantly involves deep soft tissue and skeletal muscle of the lower extremities, whereas unusual sites such as the head and neck, including the orbit and tongue, are more frequent in younger children.[29] The key histologic features include intermediate to large polygonal cells with a granular, eosinophilic cytoplasm, nested within surrounding fibrovascular septa that impart an alveolar pattern. However, according to Williams et al[39] up to 40% of ASPS have variant nonalveolar patterns making histologic distinction difficult. Although once speculated to have both neuroectodermal lineage (expression of NSE and chromogranin) and myogenic lineage (expression of actins, myosins, and less frequently desmin), ASPS is now best defined by molecular confirmation of the unbalanced ASPSCR1/TFE3 fusion transcript that involves a nonreciprocal translocation der(17)t(X;17)(p11;q25), which has greatly aided to the diagnostic armamentarium of this tumor. The recent addition of the immunohistochemical stain for the TFE3 protein (nuclear transcription factor binding to immunoglobulin heavy constant-m enhancer 3) may be a sensitive surrogate to FISH or RT-PCR.[40-43] It is a polyclonal antibody that binds to the carboxy terminal end of the TFE3 fusion chimera in both ASPS and the TFE3 translocation positive pediatric renal carcinomas with a nuclear staining pattern and shows a high sensitivity (97.5%) and specificity (99.6%).[40] While TFE3 can show reactivity in granular cell tumors, this distinction is readily apparent by histology. Discrete granular cytoplasmic expression with CD147 (monocarboxylate transporter 1) is also reported in ASPS, granular cell tumors, and metastatic clear cell sarcoma of the kidney, among other tumors, but lacks the sensitivity and specificity of the unbalanced fusion transcript and TFE3 immunoreactivity.[42]

Hepatoblastoma

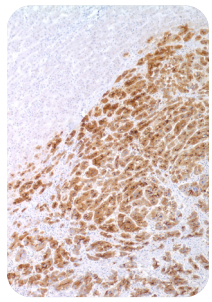
Hepatoblastoma (HB) is the most frequent pediatric liver malignancy but represents only about 1% of all childhood tumors. It is predominantly a tumor of early childhood with the vast majority occurring under 5 years of age. HB is classified broadly into epithelial and mixed epithelial and mesenchymal with or without heterologous elements. Under the epithelial type the subtypes are well-differentiated fetal with low mitotic activity, crowded fetal with mitoses, embryonal, pleomorphic/poorly differentiated, small cell undifferentiated, epithelial mixed, cholangioblastic, and epithelial macrotrabecular pattern.[44,45] The morphologic patterns of this tumor reflect histologic stages of hepatic development/differentiation as delineated in Ranganathan's detailed histologic and immunophenotypic classification[45] which has been recently incorporated into the International Pediatric Liver Tumor Consensus Classification.[44]

Briefly, the well-differentiated fetal with low mitosis is a favorable histologic pattern if present as the sole histologic subtype and can be distinguished from normal liver parenchyma by an immunohistochemical panel including fine granular cytoplasmic expression of glypican expression and diffuse glutamine synthetase (GS) expression as compared with its limited staining of centrilobular hepatocytes in normal liver.[44,45] Glypican-3 (GPC3) at Xq26.1 is a membrane-bound heparan sulfate proteoglycan that can negatively regulate the Wnt and Hedgehog signaling pathways in both HB and nephroblastoma, and is important in embryonic cell growth and differentiation. There is reported staining also present in non-neoplastic nodular regenerative hyperplasia and familial cholestatic disease with small-fetal type hepatocytes, and some reports of staining in hepatobiliary RMS.[44-46]

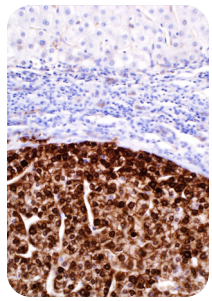
GS serves as a differentiation marker and as a downstream target of the activated Wnt signaling pathway and is more commonly expressed in fetal subtypes with less staining seen in embryonal and small cell undifferentiated subtypes.[44,45,47] In addition, the fetal epithelial subtypes typically overexpress β-catenin with diffuse cytoplasmic and/or nuclear expression, with more consistent nuclear expression in the crowded fetal type, which also shows a more coarse cytoplasmic expression of GPC3.[44,45] The embryonal subtype (resembling hepatocytes at 6 to 8 week gestation) has a more primitive "small round blue-cell" tumor appearance and can share some histologic overlap with metastatic nephroblastoma, NB, or PNET. Like the crowded fetal subtype,



TFE3



Glypican-3



Glutamine Synthetase

Wilms Tumor is the most common renal cell malignancy in children, with the vast majority occurring under 10 years of age.

it also typically shows diffuse coarse cytoplasmic expression of GPC3 and nuclear β-catenin, although expression with GS is usually negative or only variable positive.[44,45]

Another diagnostic challenge in the context of other primitive small round blue-cell tumors is the small cell undifferentiated epithelial subtype, which unlike the embryonal subtype, shows a more primitive, discohesive pattern with increased mitoses and occasional foci with anaplastic cytology. Its immunoprofile is positive for vimentin and cytokeratin (i.e., CK 19) inclusions but typically lacks staining for GPC3 and GS, along with alpha-fetoprotein and Hep Par-1 expression.[44,45] Experience suggest that the only reliable marker is strong, diffuse nuclear staining with β-catenin.[44,45] While some rhabdoid-like cells in the small cell variant may lose INI-1 expression, most retain their nuclear reactivity. Only a subset of pure small cell HB loses their expression of INI-1.[45,48]

The cholangioblastic variant is best highlighted by CK 19 along with nuclear β-catenin expression and lack of GS and GPC3 staining.[44,45] The mixed epithelial and mesenchymal HB subtype contains both epithelial and mesenchymal components, with variable amounts of osteoid, chondroid, muscle, adipose, and primitive spindle cell components. The epithelial component in mixed HB shares an immunophenotype with the pure epithelial HB, whereas the mesenchymal elements will often show nuclear β-catenin expression, thus helping to differentiate it from the chemotherapy-induced secondary mesenchyme differentiation.[44,45] A final HB histologic subtype is called “teratoid” or HB with heterologous elements, which by definition contains a neural melanocytic (neuroectodermal) component and may also show mesenchymal and heterologous epithelial components. The neuroectodermal component typically does not display nuclear positivity with β-catenin.[44,45,49]

Importantly, while CITED1 is undetectable in normal human adult livers, 36 of 41 (87.8%) hepatoblastoma specimens expressed CITED1, where it is enriched in epithelial mixed embryonal/fetal (EMEF) specimens compared to specimens of pure fetal histology.[64]

Wilms Tumor

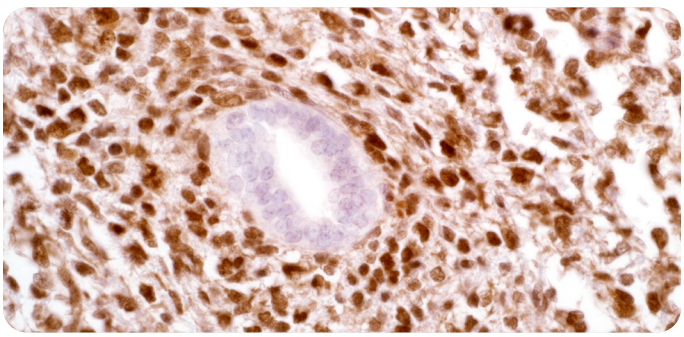
Commonly known by the eponym Wilms Tumor (WT), nephroblastoma is an embryonic malignancy thought to derive from transformed clonal renal stem cells which remain in their embryonic multipotent state. WT is the most common renal cell malignancy in children, with the vast majority (95% to 98% of cases) occurring under 10 years of age and with a slight female predominance.[50] It rates among the top 10 pediatric malignancies. The key histologic features include a triphasic pattern of epithelial (immature tubular differentiation), variable amounts of stroma (renal interstitial/stromal counterpart with occasional heterologous elements), and blastema, which represents the “small blue-cell” component of WT.

Blastema-predominant tumors create diagnostic confusion with other pediatric neoplasms showing

round to oval cells with scant cytoplasm, fine chromatin, overlapping nuclei, and small to inconspicuous nuclei. There are multiple blastema-only growth patterns, but the most common and specific ones include: nodular/serpentine pattern, invasive diffuse pattern, and basaloid. Most WT are considered to have "favorable histology" provided they lack anaplastic features, defined by hyperchromatic/aneuploid nucleomegaly, with nuclei at least three times the size of adjacent nonanaplastic nuclei, and/or atypical mitoses (i.e., multipolar, clearly aneuploid mitotic figures).

Historically, the cases with unfavorable histology represent about 5% to 10% of WT and are more frequent in children 36 months of age and older, as well as in nonwhite ethnicity.[51] The utility of immunohistochemistry in WT is limited, as the staining is not typically specific and various diagnostic components are readily identifiable by H&E staining. The blastema component is positive for vimentin and CD56; cytokeratin expression is seen when more advanced tubular differentiation is present.[1,52] The presence of transcription factor Wilms tumor 1 (WT1) can be detected in nuclei of the blastema and primitive epithelial components, using a wild-type polyclonal antibody to both the carboxy and amino terminal ends, whereas DSRCT reacts predominately only with monoclonal antibody to the carboxy terminal end, given its fusion transcript. Muscle markers such as desmin may be helpful in identifying areas of skeletal muscle differentiation and myogenin/MyoD1 may further clarify the extent of rhabdomyoblastic elements.

WTs with a predominate primitive stromal pattern have been shown to have expression of both BCL2 (cytoplasmic) and WT1 (nuclear) expression, which may help differentiate a primary spindle cell Wilms from a renal SSs [BCL2(+)/WT1(-)], clear cell sarcoma of kidney (CCSK) [BCL2(+/-)/WT1(-)], and cellular mesoblastic nephroma [BCL2(-)/WT1(-)].[53]



CITED1

Wilms tumors are thought to arise from abnormal postnatal retention and dysregulated differentiation of nephrogenic progenitor cells that originate as a condensed metanephric mesenchyme within embryonic kidneys. The transcriptional regulator CITED1 (CBP/p300-interacting transactivators with glutamic acid [E]/aspartic acid [D]-rich C-terminal domain) is expressed exclusively in these nephrogenic progenitor cells and is downregulated as they differentiate to form nephronic epithelia. Unlike the predominantly cytoplasmic subcellular localization of CITED1 in the normal developing kidney, CITED1 is clearly detectable in the nuclear compartment of Wilms tumor blastema.[65] CITED1 is expressed in blastema in 100% of the WTs with this component present. It is also expressed in 64% of the epithelial WT elements and 48% of stromal WT elements.[66]

Other Renal Tumors

Non-WTs account for approximately 15% of childhood renal tumors and include mesoblastic nephroma, renal cell carcinoma (RCC), rhabdoid tumor, clear cell sarcoma of the kidney (CCSK), and on rare cases, the family of primary neuroepithelial tumors of the kidney (NETK), which include primary renal PNET and small cell carcinomas. Mesoblastic nephroma, given its morphological and genetic features is discussed under infantile fibrosarcoma. Pediatric RCC are rare (2%) and are mostly comprised of so-called translocation-associated RCC. These are most common in older adolescents but can occur in the pediatric-age group.[54] A handful of translocation RCC in adults have been noted to have a more aggressive course compared with their pediatric counterpart.[55] These tumors have varied histologic arrangements in tubules, nests, acini, or papillae, but the most consistent finding includes voluminous clear, eosinophilic cytoplasm with prominent nucleoli (typically Furman grade 3).

Unlike conventional RCC, translocation RCC lack cytokeratin expression and almost universally show nuclear reactivity with the TFE3 antibody, caused by the same transcription factor gene (TFE3) located at Xp11.2 seen in ASPS. These translocation tumors typically also express CD10 with variable to weak RCC immunoreactivity, but do not show expression for EMA, WT1, and HMB-45.[54]

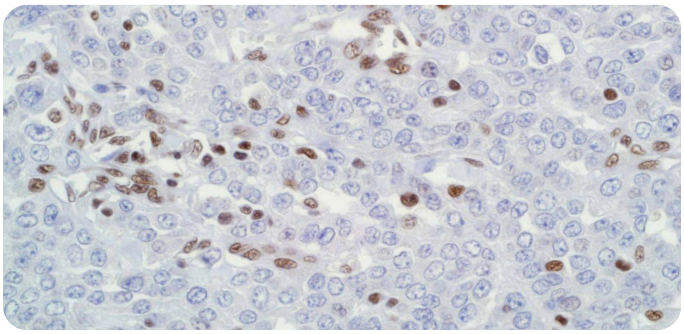
Because these tumors can show histologic overlap with other RCC, confirmation with TFE3 immunostains and molecular translocation are needed for definite identification, especially for variant translocation cases.

CCSK, also known as bone-metastasizing renal tumor of childhood, accounts for <5% of primary pediatric renal tumors and is believed to derive from a clonal undifferentiated mesenchymal cell.[14] There are numerous morphologic patterns but key histologic features include sheaths, nests, and cords of 6 to 10 cells thick separated by a fine fibrovascular meshwork. The proliferating cells have inconspicuous cytoplasm whose vacuolization imparts the appearance of clear spaces; nuclei are small and feature finely dispersed chromatin.

Rare cases of CCSK have also shown positive staining with CD147[42] and BCL2 but are negative with WT1 staining.[67] Most cases are negative for cytokeratin, EMA, desmin, and CD99. However, rare cases of CD99-positive primary NETK with clear cell sarcoma-like foci have been described and should be differentiated from pure CCSK, which are CD99 negative.[56]

Malignant Rhabdoid Tumors

Malignant rhabdoid tumors (MRTs) are also highly aggressive, high-stage malignancies seen as primary tumors in certain preferred sites such as kidney, central nervous system, and soft tissues of young children, with an age at presentation between 8 and 17 months. MRT may constitute only about 2% of pediatric renal tumors but ought to be histologically distinguished from other renal neoplasms. The key histologic features include a monomorphous population of discohesive cells with eosinophilic cytoplasm and a large, paranuclear, glassy, cytoplasmic pseudoinclusion of intermediate filaments, and an eccentric nucleus with a prominent nucleolus. MRTs are defined by the loss of SMARCB1 at 22q11.2 (SNF5, INI-1), a component of the SWI/SNF chromatin remodeling complex. Positive immunohistochemical stains in MRTs include vimentin, which is most consistently expressed in a paranuclear dot-like pattern, followed by focal EMA, cytokeratin, SMA, and muscle specific actin with variable expression of desmin.



INI-1

Neuroectodermal expression with NSE, CD57, synaptophysin, and/or CD99 is also seen, along with variable expression of S-100. However, the defining immunostain is loss of nuclear staining for INI-1, with retained nuclear staining of the non-neoplastic elements, including endothelial and stromal cells, which serve as an internal positive control. The majority of MRT demonstrate aberrations of the gene SMARCB1, which transcribes the INI protein responsible for chromatin-histone remodeling for transcription regulation. Biallelic loss of the tumor suppressor function of this gene can occur either sporadically in the tumor, or less commonly as a result of a constitutional deletion and loss of the subsequent normal allele in the tumor. When compared with other pediatric malignancies, the loss of nuclear INI-1 expression is fairly specific to rhabdoid tumors, although certain tumors such as a subset of SS, epithelioid sarcoma, and pure small cell subtype HB may also show complete to partial INI-1 loss.[34,48,57]

Although other authors have shown that the majority of molecularly confirmed SS cases (75%) may demonstrate reduced to complete INI-1 loss of expression, a corresponding genetic alteration of SMARCB1 is typically not present.[29,34] A growing number of tumors have been reported to have loss of INI-1 immunoreactivity[29] but thus far it has been retained in EWSFT, DSRCT, WT, clear cell sarcoma of the kidney, congenital mesoblastic nephroma, undifferentiated sarcoma, and RMS.

Congenital/Infantile Fibrosarcoma And Cellular Congenital Mesoblastic Nephroma

Congenital/infantile fibrosarcoma (CIFS) and cellular congenital mesoblastic nephroma (cellular-CMN) are included together, given the increasing amount of molecular data establishing these tumors as a shared entity[58] rather than two separate tumors with a similar translocation (as seen with ASPS and the Xp11-translocation associated RCC).

CIFS/cellular-CMN is a tumor of infancy with a mean age of <2 months, making it the most common mesenchymal malignancy under 2 years of age.[59] Many cases are detected in utero with improved ultrasound imaging. It is now recognized that cellular-CMN is CIFS in a renal location. Outside the kidney, the most common location of CIFS is within the distal extremities, but cases occurring in the head, neck, and trunk are not uncommon.

The key histologic findings of CIFS/cellular-CMN include a circumscribed but unencapsulated mass of tightly packed round to elongate monomorphic cells with moderate eosinophilic cytoplasm and vesicular nuclei with a high proliferative rate. In contrast, classic-CMN has an irregular, interdigitating border with longer interlacing fascicles of plump spindle cells intermixed with a variable collagenous stroma and thin, dilated blood vessels. The dual pattern of classic and cellular types is seen in about 20% of renal cases.[60] All patterns of these tumors express variable reactivity with vimentin, SMA, and desmin.

Only demonstration of the recurrent translocation t(12;15)(p13;q26), by which ETV6 transcriptional regulator gene (12p13) fuses with the TRK domain of the neurotrophic TRK receptor type 3 (NTRK3) at 15q26, can accurately define this tumor entity.[61]

Pleuropulmonary Blastoma

Pleuropulmonary blastoma (PPB) is a rare childhood primary intrathoracic neoplasm categorized into three main pathologic types (I to III). The tumor, composed of immature pleuropulmonary mesenchyme, can arise from the lung, pleura, or mediastinum. While the cell origin may be an early primitive interstitial mesenchymal element, the exact derivation remains a question of debate. Both sexes, typically 5 to 6 years old and younger, are affected, and it is advocated that any multilocular cyst in a child less than 3 years old should be thoroughly examined because early or type I PPB can have varied histologic patterns.[62] The general features are those of a cystic neoplasm composed of a benign mostly flattened alveolar type lining with a heterogenous wall composition, which can range from a condensed cambium layer of immature malignant

mesenchyme to a sparse subepithelial collection of primitive cells to a more acellular collagenous wall. While PPB-I does share some overlapping histologic features with cystic pulmonary airway malformations, there is no consensus regarding its possible origin from airway malformations,[63] or whether the two should be considered separate entities.[62] Myogenin, MyoD1, and desmin can help highlight the rhabdomyoblastic differentiation of the small scattered primitive mesenchymal cells and condensed cells of the cambium layer, as not all cases show distinctive skeletal muscle differentiation by histology alone. However, demonstration of skeletal differentiation, even by immunohistochemistry is not a consistent finding.[62]

Nodules or bands of fibroblast-like spindled cells may be highlighted by vimentin and small nodules of cartilage found in association with the spindle cells can be highlighted with S-100 if not readily apparent by histology. Rare PBP type I cases have been described with only the fibroblast-like spindled cells and cartilage present in the multilocular lung cyst.[62] The Ki-67/MiB proliferation index of the primitive mesenchymal cells is variable with a high index in the cambium layers (80% to 90%), but there is inconsistent and variable expression in the more dispersed mesenchymal spindle cells (4% to 30%). In contrast, there is an increased proliferation index in those PPB showing progression to both types II and III.[62] Type II PPB has sarcomatous overgrowth, with solid features intermixed with cystic areas to produce an intermediate phenotype. Type III PPB is a purely solid neoplasm with complete sarcomatous overgrowth. The solid components of both type II and III have characteristic cellular islands of blastema encircling loose immature mesenchyme, along with variable amounts of cartilage, rhabdomyoblasts, and anaplastic cells. Immunohistochemical stains as described above may further highlight the rhabdomyomatous differentiation. In familial PPB, these lung neoplasms are harbingers of other dysplasias and malignancies in the patient and/or in closely related kindred (i.e., cystic nephroma, RMSs, ovarian Sertoli-Leydig, medulloblastoma, thyroid nodules, hamartomatous intestinal polyps, etc). Recently, the familial PPB locus has been mapped to a germline aberration in chromosome 14q32. For the other 80% of nonfamilial PPB cases, gains of chromosome 8, including trisomy 8, have emerged as a recurrent cytogenetic abnormality, even in type 1 PPB, whereas trisomy 2 and 17p deletions have been reported less frequently in sporadic cases.

Intended Use:

These products herein are intended for laboratory use in the detection of their respective proteins in formalin-fixed, paraffin-embedded tissue stained in qualitative immunohistochemistry (IHC) testing. These products are not a stand-alone diagnostic, and cannot be used for diagnosis, treatment, prevention, or mitigation of disease.

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32740 Ver. 0.0 MS_BR6755EN 09/2020