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Original Article

An Analysis of Pediatric Round Cell Tumors Highlighting the Spectrum of Differential Diagnosis – A Single Center Experience and Systematic Review of Literature

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Abstract

Introduction: Pediatric round cell tumors (PRCT) are extremely aggressive tumors composed of similar histology comprising undifferentiated primitive cells with variable histogenesis. Differential diagnosis is challenging in these tumors and needs a holistic approach comprising histology and immunohistochemistry (IHC). A definite diagnosis is essential for therapeutic and prognostic implications.

Aims: Analyzing the PRCT to outline an approach toward accurate diagnosis and exclusion of the close differentials.

Materials and Methods: This is a 1-year retrospective study at Homi Bhabha Cancer Hospital over a period of 1 year, and it included PRCT cases without prior chemotherapy. Patient demographics and imaging data were collected, and tissue slides were reviewed for histomorphology and IHC, including tumor type, differentiation, and marker status.

Results: In the study duration, a total of 121 cases of PRCT were reported with male preponderance and a mean age of 6.7 years. Wilm's tumor was the most common PRCT, followed by Ewing's sarcoma, non-Hodgkin lymphoma, and rhabdomyosarcoma. Based on clinicoradiological correlation and histomorphological findings, a panel of markers such as CD99, friend leukemia integration-1, CD45, CD3, CD20, myogenin, MyoD-1, desmin, synaptophysin, chromogranin, CD56, AE1/AE3, WT1, CK19, epithelial membrane antigen, October 3/4 were applied. Based on immunohistochemical expression, an approach toward the diagnosis of PRCT was outlined.

Conclusion: PRCTs are aggressive childhood and adolescent tumors with undifferentiated morphology and several close differentials. Diagnostic accuracy improves with IHC alongside histomorphology and clinicoradiological findings, whereas cytogenetic and molecular tests aid in challenging cases. Precise classification guides treatment decisions – chemotherapy, radiotherapy, resection, or targeted therapy, and informs prognosis.

Key words: Histopathology, Immunohistochemistry, Pediatric round cell tumor

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INTRODUCTION

Every year, around 215,000 malignancies are identified in children under the age of 15, resulting in an estimated 80,000 cancer-related deaths globally.[1] In India, cancer is the ninth leading cause of mortality among children aged 5–14.[2]

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Because of the increasing trend of childhood malignancies, it has become necessary to correctly diagnose and treat this disease. A large majority of pediatric solid tumors comprise small round cell tumors. Pediatric round cell tumors (PRCT) are a group of highly aggressive tumors with similar histology but diverse histogenesis.[3]

These are characterized by small, round, undifferentiated cells and are challenging to diagnose due to their lack of differentiation. Differential diagnosis is difficult due to the presence of undifferentiated primitive cells.[4,5]

This category of tumors includes retinoblastoma (RB), neuroblastoma, hepatoblastoma (HBL), nephroblastoma, rhabdomyosarcoma (RMS), Ewing sarcoma, peripheral neuroectodermal tumor, desmoplastic small round cell tumor (DSRCT), and non-Hodgkin lymphoma (NHL).[6]

It is important to identify the specific type of small round cell tumors because they are genetically and biologically different from each other.[7] Light microscopy with Haematoxylin and Eosin (H and E) staining is often ineffective for diagnosing this group of tumors. Furthermore, their clinical features sometimes overlap, making diagnosis challenging in some circumstances. Therefore, a multiparameter approach comprising histology and immunohistochemistry (IHC) is essential in most cases in combination with cytogenetics and molecular studies when necessary.[8]

A definite diagnosis is important for therapeutic and prognostic implications.[3]

In this study, we aim to analyze the PRCT in a tertiary care cancer center in north India and hence outline an approach toward accurate diagnosis and exclusion of the close differentials.

MATERIALS AND METHODS

This was a retrospective observation study conducted in the Department of Pathology at Homi Bhabha Cancer Hospital, Varanasi, over a period of 1 year (2018–2019), wherein all the cases reported as PRCT were included. The cases with prior chemotherapy were excluded from the analysis. Details regarding the age, gender, radiology, and PET scans were collected from the patient's electronic medical records. The corresponding biopsy or excision specimen's slides were reviewed for the histomorphological details and immunohistochemical analysis, namely the type of tumor, its differentiation, positivity, and negativity of IHC. Statistical analysis was done on the collected data.

RESULTS AND DISCUSSION

A total of 121 PRCT patients were reported during the study duration. The mean age of patients was 6.7 years, ranging from 2 months to 18 years. Male preponderance (65.3%) was observed in the study population, and most of the patients (76.9%) were in the first decade of life [Figure 1]. The most common PRCTs were Wilms tumor (29.8%), followed by Ewing sarcoma (18.2%), NHLs (18.2%), and RMS (13.2%) [Figure 2]. In the younger children (≤ 10 years), Wilms tumor, Ewing sarcoma, and RMS were frequent, and among adolescents, NHLs were common. Among these, 32.2% ($n = 39$) of cases had distant metastasis at presentation. Wilms tumor patients most frequently had metastases, followed by Ewing sarcoma, and the lungs were the most common organs involved (51.3% of 39 cases).

IHC analysis was performed on 95 cases after excluding 26 cases with prior history of chemotherapy (two cases

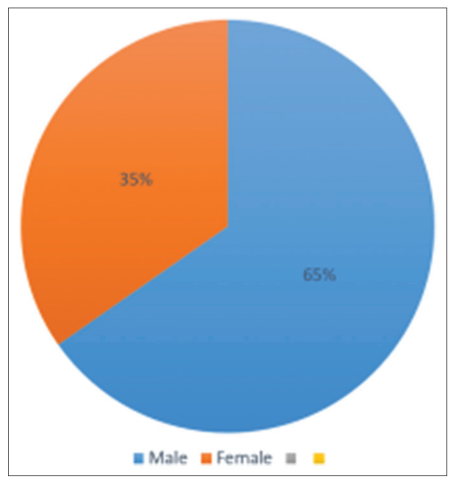

Figure 1: Pi-chart depicting gender distribution of cases

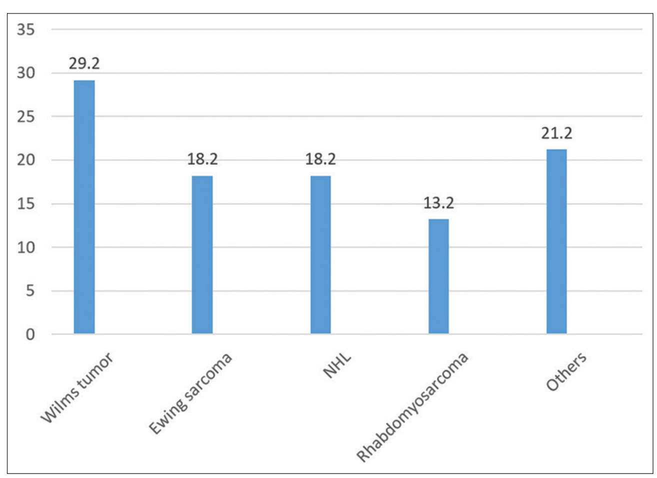

Figure 2: Graph depicting the percentage of various pediatric round cell tumors in the present study

of HBL, and 24 cases of Wilms tumor). The usual IHC markers done (based on the case scenario) included CD99, friend leukemia integration (FLI-1), CD45, CD3, CD20, myogenin, MyoD-1, desmin, synaptophysin, chromogranin, CD56, AE1/AE3, WT1, CK19, epithelial membrane antigen (EMA) October 3/4, and vimentin. Additional markers were done in a few cases.

Among 22 Ewing sarcoma cases, all were positive for CD99 (100%), and 17 (89.5%) were positive for FLI-1. However, CD99 is non-specific, and it was positive in five embryonal RMS (ERMS) and one Wilms tumor [Figure 3]. Perinuclear dot-like positivity was seen in four other tumors. FLI-1 is usually positive in 95% of Ewing sarcoma cases, whereas when the fusion partner is different, it may be negative. Thus, warranting molecular analysis. FLI-1 was positive in two lymphomas and focally positive in one case of undifferentiated sarcoma [Figure 3].

In RMS, desmin was positive in 13 (92.9%) cases, myogenin in 10 (71.4%) cases, and MyoD-1 in 11 (78.6%) cases. Myogenin was focal in three cases and diffuse in seven cases. It is observed to be diffuse in alveolar RMS and focal in embryonal RMS. MyoD-1 is more specific for RMS, whereas desmin is the most sensitive. Desmin was positive in two cases of Wilms tumor and focally positive in mesenchymal chondrosarcoma.

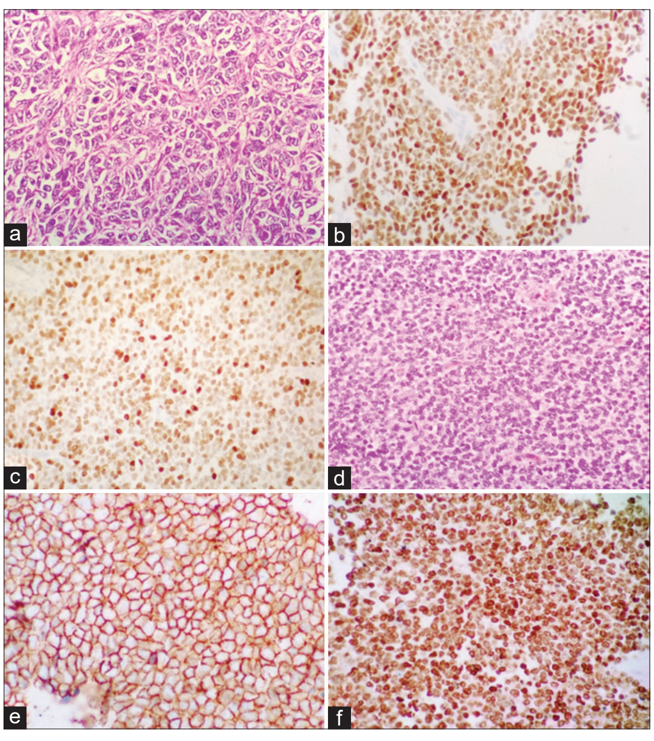

Figure 3: (a) Synovial sarcoma: Microsection shows the round cell morphology of the tumor cells having clear cytoplasm and brisk mitosis, H and E, 40×. (b) On immunohistochemistry, tumor cells are diffusely positive for TLE-1. (c) Diffuse nuclear positivity is seen for SS18. Ewing sarcoma: (d) Diffuse sheets of small round blue cells, H and E, 40×. (e) Strong membranous positivity is seen for CD99. (f) NKX2.2 is positive in the tumor cell nuclei

In HBLs, CD19 was diffusely positive in one case and focally positive in two cases. AE1/AE3 was also positive. Neuroblastomas showed positivity for synaptophysin (80%), chromogranin (40%), and CD56 (60%). Among these, synaptophysin was most sensitive, and chromogranin was most specific. Synaptophysin was also positive in four cases of Ewing sarcoma and focally positive in one case of undifferentiated sarcoma. CD56 was positive in synovial sarcomas as well; however, diffuse positivity for TLE1 helped in distinguishing poorly differentiated synovial sarcoma cases with round cell morphology [Figure 3].

Among the NHLs, CD45 was diffusely positive in all cases (100%). CD20 was positive in B-cell lymphomas (54.5%), including Burkitt lymphomas, B-cell lymphoblastic lymphomas (LBL), and large B-cell lymphomas. CD3 was diffusely positive in T-cell LBL (22.7%). In other tumors, only the background cells stained for CD3 and CD20, but it was not a diffuse staining pattern [Figure 4].

In Wilms tumor, WT1 was positive in 66.7% of cases along with either desmin, AE1/AE3, or focal EMA. However, WT1 can also be positive in DSCRT, wherein neuron-specific enolase (NSE) positivity favors the diagnosis of the latter. The germ cell tumor was positive for Oct3/4 and negative for other markers. Clear cell sarcoma of the kidney was diagnosed by exclusion when synaptophysin, chromogranin, CD56, CD99, leukocyte common antigen, and desmin were negative.

Based on the study of immunohistochemical expression in PRCT, an approach is outlined for definite diagnosis in Figure 5.

Discussion

The category of round cell tumors includes a varied group of tumors with different treatment protocols and prognoses. Despite their identical morphology, they differ from one another genetically and biologically. Light microscopy alone cannot categorize these tumors. Hence, additional techniques, such as IHC, electron microscopy, cytogenetics, and molecular profiling, are necessary for their differentiation.[9]

Before relying on IHC for diagnosis, it is important to thoroughly examine the H and E sections in a clinicoradiological setting. The majority of malignant undifferentiated neoplasms can be diagnosed histologically using an extended panel of antibodies.

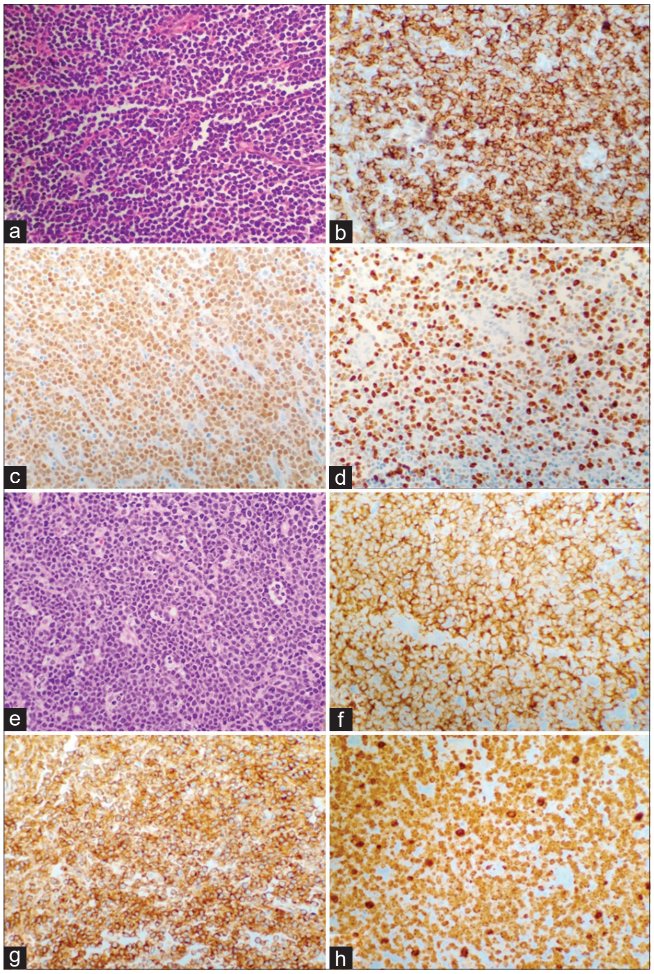

Figure 4: (a) Lymphoblastic lymphoma: Microsection shows sheets of malignant small round cells (H and E, 20×). (c) On immunohistochemistry, tumor cells are diffusely positive for CD20. (c) TDT is diffusely positive in all the tumor cell nuclei. (d) Ki-67 proliferative index is >90%. Burkitt lymphoma: (e) Microsection shows sheets of small tumor cells with numerous tangible body macrophages, (H and E, 20×). (f) On immunohistochemistry, tumor cells are diffusely positive for CD20. (g) CD10 is positive in the tumor cells. (h) c-myc is diffusely positive in all the tumor cell nuclei

In this study, we have studied 121 cases of PRCT with their morphological and immunohistochemical features, along with the diagnostic challenges we face in diagnosing this group of tumors.

The mean age of patients was 6.7 years, ranging from 2 months to 18 years. Male gender was commonly affected as compared to females (M: F = 1.8:1), similar to another study by Harmon *et al.* in which the male-to-female ratio was 4:1.[5]

The most common PRCT in the present study was nephroblastoma/Wilms tumor. However, in another similar study by Bharathi *et al.*, NHL was most common and nephroblastoma was the second most common type of PRCT, accounting for 27%.

NHL constituted 18.2% of the overall PRCT in the present study and also constituted the most common PRCT among the adolescent population group.

Nephroblastoma/Wilms' tumor (WT) is the most common pediatric renal tumor, appearing as a solitary nodule, multifocal unilateral lesions, or bilateral tumors. Typically, WT has three histological components: blastemal, epithelial, and stromal.[10] WT manifests in different patterns due to the various lines and degrees of differentiation of its components. Pre-operative chemotherapy used in SIOP studies leads to chemotherapy-induced alterations that can affect 0-100% of the tumor and alter its histological characteristics.[11]

Classical triphasic WT rarely presents diagnostic difficulties for pathologists. However, when only one component is present, especially in a small biopsy specimen, the differential diagnosis may include renal cell carcinoma, metanephric adenoma, and hyperplastic nephrogenic rest for epithelial elements and clear cell sarcoma of the kidney, mesoblastic nephroma, and synovial sarcoma for stromal elements.[10]

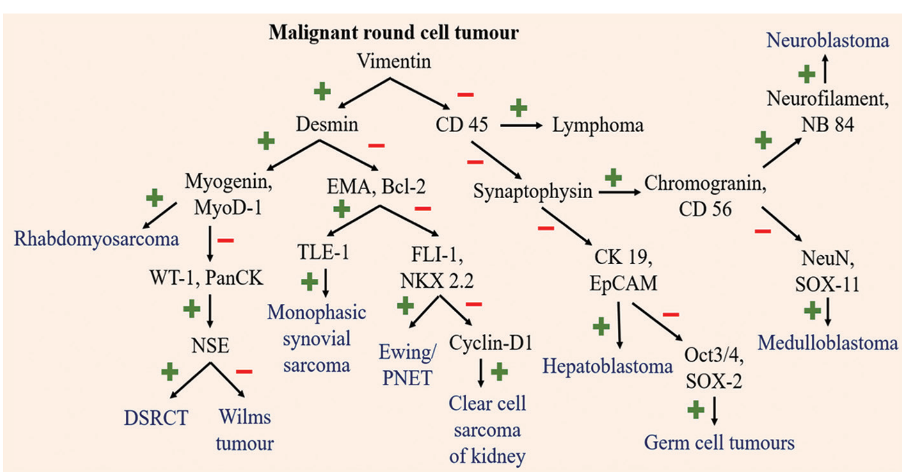

Figure 5: Flowchart depicts the immunohistochemical approach for pediatric round cell tumor

In cases with pure blastemal component constituting the majority of the tumor part, the differentials include other round cell tumors such as neuroblastoma, Ewing sarcoma of the kidney,[12] DSRCT,[13] and synovial sarcoma.[14]

In such circumstances, IHC and molecular investigations are crucial for determining the accurate diagnosis.

Both blastemal components of WT and Ewing sarcoma can show CD99 positivity, but CD99 is diffusely expressed in the case of Ewing sarcoma, while it is focal in WT.[12] Furthermore, Ewing sarcoma is positive for NKX2.2, which is negative in WT.[11] In the present study, too, in cases of blastemal predominant WT, we have taken the help of IHC markers such as PAX8 and WT1 to differentiate it from other round cell tumors.

DSRCT shares many immunohistochemical characteristics with blastemal-type WT, but it is a rare tumor in this location. Hence, the diagnosis of DSRCT should only be made in the kidney if genetic investigations reveal the EWS-WT1 t(11;22)(q13;q12) translocation.[13]

Another common type of PRCT is neuroblastoma, which typically exhibits high catecholamine levels, and histologically, it is composed of non-overlapping nuclei with coarse salt and pepper chromatin. Both tumors may be positive for NSE and CD56; however, the WT1 marker is negative in neuroblastoma.[10]

Another common PRCT is Ewing sarcoma, which accounts for 6–8% of all primary malignant bone tumors in children, and the second most prevalent bone tumor after osteosarcoma.[11]

Ewing sarcoma typically affects the diaphysis and diaphyseal-metaphyseal regions of the long bones, pelvis, and ribs. Extraskeletal Ewing's sarcoma accounts for 12% of cases.[15]

Microscopically, Ewing sarcoma is composed of solid sheets of small round tumor cells with round nuclei bearing coarsely granular chromatin; inconspicuous nucleoli; and sparse, indistinct, transparent to palely eosinophilic cytoplasm.[11] Positive immunohistochemical markers include CD99, which shows diffuse membranous positivity, and NKX2.2 2 which is a nuclear marker. However, CD99 is not specific for Ewing sarcoma, and it can be positive in other PRCTs such as round cell sarcomas with EWSR1-non-ETS fusions,[16] Synovial sarcomas,[17] T lineage acute lymphoblastic leukemia,[18] along with a wide variety of tumors. NKX2.2 is highly sensitive but moderately specific for Ewing sarcoma, as it can be positive in other tumors, such as well-differentiated neuroendocrine tumors and small cell carcinoma.[19,20]

RMS constituted 13.2% of the PRCTs in the present study. ERMS is the most common subtype in the pediatrics and adolescent groups and most prevalent in the head and neck region, encompassing the nasal and oral cavities, as well as the orbit and middle ear, and also present in the paratesticular soft tissues and the genitourinary tract.[21] ERMS shows diverse cellularity, ranging from stellate cells in an extensive myxoid stroma to sheets of poorly differentiated, tightly packed cells with spherical or slightly angulated nuclei.[11]

All RMSs have skeletal muscle differentiation, which can be validated by IHC expression of desmin, myogenin, and/or MYOD1.[11]

Poorly differentiated synovial sarcomas, which may exhibit round cell morphology, can be reliably distinguished through a panel of immunohistochemical markers, including TLE1, CD56, BCL2, and CD99, in conjunction with the fusion-specific oncoprotein SSX-SS18.[11]

Lymphomas rank third among all cancers in children, with Hodgkin lymphoma making up 6% and NHL about 7% of all cancers in this age group.[11]

The majority of pediatric lymphomas are precursor B-cell or T-cell leukemias/lymphomas, high-grade B-cell lymphomas such as diffuse large B-cell lymphoma (DLBCL), and anaplastic large cell lymphoma (anaplastic lymphoma kinase-positive).[22,23]

In the present study, NHL was the commonest PRCT in the adolescent age group and included Burkitt's lymphoma, LBL, and diffuse large B-cell lymphoma. NHL was further categorized using an IHC panel that comprised CD20, CD3, CD10, BCL2, BCL6, CD5, CD23, MUM-1, and Ki67. Two cases of Burkitt's lymphoma were detected using clinical data and markers such as CD 20, CD 10, and BCL-6 along with Ki67 proliferation index.

LBL is the second most frequent kind of (NHL) in childhood and adolescence, with the majority being T LBL (75–80%) and the remaining being B LBL (20–25%).[22]

Histologically, LBL shows a small, round, blue cell infiltrate. Immunonophenotype, along with cytogenetics, is required to differentiate it from other small round cell tumors. The initial panel of CD45, along with TdT and lineage-specific markers for B and T cells, is helpful in diagnosing these entities.

Another NHL with round cell morphology is Burkitt's lymphoma, which is characterized by a diffuse monomorphic population of medium-sized cells with many mitotic figures and a starry-sky pattern due to the presence of tingible-body macrophages.[11]

The tumor cells are molded against each other with squared-off, round nuclei and multiple medium-sized nucleoli, which are paracentrically located, resembling centroblasts.

IHC, such as CD45, Pan B-cell markers such as CD20, CD79a, and PAX5, germinal center markers such as CD10 and BCL6, and MYC protein expression in correlation with morphological features are helpful in distinguishing this entity from other PRCT.[11]

Another common NHL in the present study was DLBCL, which constitutes dense sheets of blastic cells with centroblastic and immunoblastic patterns, leading to confusion with LBL.[11]

They can also sometimes show a starry sky appearance like Burkitt's lymphoma.

Therefore, the diagnosis of DLBCL-NOS in a childhood, adolescent, and young adult patient should predominantly exclude lymphoblastic and Burkitt lymphomas.[11]

TdT can be used to distinguish LBL from DLBCL-NOS. Differentiating DLBCL with starry sky appearance morphology from Burkitt lymphoma can be challenging, as both are positive for B cell markers. DLBCL has more variable cytological morphology compared to Burkitt's lymphoma, and the Ki67 proliferation index is not as high as Burkitt's lymphoma. Still in confusing cases, genetic testing for MYC rearrangement is advised.[11]

Common PRCT occurring in the posterior fossa of the brain is medulloblastoma. It is the second most frequent central nervous system malignant tumor in childhood, after high-grade glioma, accounting for roughly 20% of all intracranial neoplasms in this age group.[24]

The median patient age upon diagnosis of medulloblastoma is 9 years, with peaks in incidence at 3 and 7 years of age.[25]

Medulloblastomas should now be classified based on both molecular and histological criteria. Their molecular classification reflects biological heterogeneity, which can be proved by clustering medulloblastomas into groups using transcriptome or DNA methylation profiling.[11]

Medulloblastoma has four main histological subtypes. The classical type shows sheets of undifferentiated cells with high mitoses and occasional Homer Wright rosettes. The desmoplastic/nodular variant has pleomorphic cells with reticulin-rich stroma and reticulin-free nodules. The extensively nodular type features enlarged, neuropil-rich nodules. The large cell/anaplastic variant shows pleomorphic cells with high mitoses, apoptosis, nuclear molding, and cell wrapping.[26]

On IHC, tumor cells are positive for NeuN and Synaptophysin. INI1 is retained in the tumor cells, which is lost in the atypical teratoid/rhabdoid tumor, which is the other close differential and can show sheets of undifferentiated cells with round cell morphology. The important diagnostic feature on histology is the presence of rhabdoid cells with well-defined cell borders and eccentrically placed nuclei with vesicular nuclear chromatin, prominent eosinophilic nucleoli, and abundant cytoplasm with eosinophilic inclusions.[27]

RB is the most prevalent intraocular cancer in children, distinguished by hyperchromatic small round blue cells with scant cytoplasm organised in sheets, nests, and trabeculae.[11]

Morphologically, RBs may be poorly differentiated, moderately differentiated (rosettes), or well differentiated (fleurettes). Flexner-Wintersteiner rosettes with central lumina are typical of RB and mimic retinal differentiation; however, they can also be found in medulloepithelioma. Homer Wright rosettes are less common in RB and are characterized by a lack of central lumen, and tumor nuclei are displaced away from the eosinophilic center.[11]

On IHC, tumor cells are positive for NSE, synaptophysin, SOX2, and MAP2. RB is easily diagnosed in correlation with clinicoradiological findings, as it is intraocular PRCT, and common differentials include lymphomas, which can be easily distinguished with the help of histomorphology and IHC.

Two cases of HBL were also reported in the present study, which is also a common differential diagnosis of PRCTs in the abdominal region. HBL is the most common pediatric liver tumor that occurs in the age group of 6 months–5 years and commonly affects the right lobe of the liver.[11]

HBLs are divided into two categories based on the components they contain: mixed HBL, which occurs when both mesenchymal and epithelial components are present, and epithelial HBL. HBLs with round cell morphology are small cell undifferentiated HBLs and Embryonal HBLs. These tumors are diagnosed by histomorphology along with clinicoradiological correlation, and IHC is rarely used.

CONCLUSION

PRCTs are the aggressive group of tumors in childhood and adolescent age groups. Wilms tumor is the most common PRCT in this region, followed by Ewing sarcoma, NHL, and RMSs. Ewing sarcoma predominates in the first decade, while lymphomas are more frequent in adolescents. Considering the fact that they have very undifferentiated morphology with a number of close differentials, the diagnostic accuracy of PRCTs can be significantly improved with the use of IHC in correlation with histomorphology and clinicoradiological findings. A stepwise immunohistochemical approach is advised, using the full panel judiciously. However, in difficult cases, cytogenetic and molecular confirmation is recommended. The aim of definite categorization of this group of tumors is to guide clinicians for the treatment modalities, whether the patient needs chemotherapy, radiotherapy, resection, or targeted therapy. Furthermore, the prognostic implications of these tumors can be different from each other.

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