International Journal of Clinical and Diagnostic Pathology

ISSN (P): 2617-7226
ISSN (E): 2617-7234
www.patholjournal.com
2022; 5(4): 74-79
Received: 04-07-2022
Accepted: 09-08-2022

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Histopathological study of pediatric solid malignant tumors in a tertiary care hospital

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DOI: https://doi.org/10.33545/pathol.2022.v5.i4b.494

Abstract
Background: Pediatric malignancies are extremely heterogeneous yet account for only approximately 1% of all tumor diagnosis. These entities are important to recognize because their clinical features are non-specific and may mimic common disorders of childhood .Pediatric solid malignant tumors are clinico-biologically distinct. They are more aggressive but usually respond satisfactorily to chemotherapy. The advanced multidisciplinary approach results in improved overall survival and a better quality of life for majority of the patients [1].
Aims & Objectives:
- To study the incidence, age and sex distribution of Pediatric solid malignant tumors.
- To study the histopathological appearances of various Pediatric solid malignant tumors.

Materials and Methods: A retrospective observational cohort study over a period of 5 years (January 2017 to September 2021) in the age group of 0-14 years was conducted in civil hospital, BJ Medical College, Ahmedabad. The data was retrieved from LIS (laboratory information system).The data consisted of information about the surgical pathology specimens received in histopathology laboratory from surgical departments. All specimen were examined macroscopically, processed by routine paraffin processing method and haematoxylin and eosin stained sections were studied microscopically.
Results: In our study of 170 malignant cases, patients were stratified in 3 age groups; 0-5 years, 6-9 years, 10-14 years.Total of 110 cases were observed among males and 60 cases among females. Most of the malignancies 67(39.4%) were observed among 0-5 years age group. Central Nervous System (CNS) malignancies 123(72.35%) was most common followed by soft tissue sarcoma, lymphoma, germ cell tumors, renal malignant tumors, bone tumors and miscellaneous malignant tumors.

Keywords: Pediatric solid malignant tumors, central nervous system malignancy, histopathology

Introduction
Pediatric solid malignant tumors poses particular challenges due to their rarity, heterogeneity, unique pathogenesis and molecular characteristics. Malignancies accounts for the major cause of death in Indian children next to infection and malnutrition. According to data from Leukemia and Lymphoma society, the most common groups of cancer in children and adolescents and young adults (CAYA) are Leukemia, tumors of the nervous system, Non-Hodgkin lymphoma, Hodgkin lymphoma and soft tissue sarcoma. The spectrum of paediatric tumors varies considerably and differs from that in adults with respect to incidence, type of tumor, underlying familial or genetic aberration and tendency to regress spontaneously [2]. For children, the International Classification of Childhood Cancer (ICCC) is used based on morphology of the tumors and is composed of 12 main groups [3].
The World Health Organization (WHO) Classification of Pediatric Tumors is rooted in a multi-layered approach, incorporating morphology, IHC and molecular characteristics. The WHO volume is organized according to organ sites and provides a single, state-of-the-art compendium of pediatric tumor types [1]. In contrast to cells successively acquiring genetic hits over time in adults, pediatric tumors are typically caused by a maturation block occurring in an immature developing cell type [5]. Tumors in children predominantly show very limited immune cell infiltration and are thus often considered immunologically "cold" tumors [6-8].Because of the unique properties of childhood cancers, they are not stratified by the topographic site rather by the histologic type. Histologic type and subtype is important for understanding etiology and progression of disease. Hence a comprehensive evaluation is required to provide an appropriate diagnosis for designing therapy and predicting prognosis of pediatric malignant tumors [9].

Aims and Objectives

- To study the incidence, age and sex distribution of Pediatric solid malignant tumors.
- To study the histopathological appearances of various Pediatric solid malignant tumors.

Materials and Methods

A retrospective observational cohort study over a period of 5 years (January 2017 to September 2021) in the age group of 0-14 years conducted in civil hospital, BJMC Ahmedabad. The data was retrieved from LIS .The material received consisted of the surgical pathology specimens and biopsy tissues fixed overnight in 10% neutral buffered formalin. Paraffin sections cut at 4-6 microns thickness and routine H&E staining was performed. The slides were examined for architecture and pattern of tumor cells, morphology of cells with nuclear and cytoplasmic characteristics. The clinical, radiological and therapeutic data from LIS records are correlated while reporting.

Results and Observation

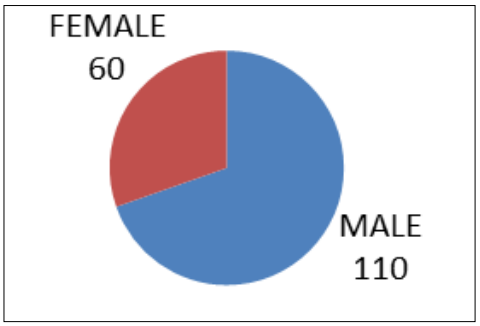
- The total number of pediatric solid malignant tumors studied were 170. The Study sample were stratified in 3 age groups: 0-5 years, 6-9 years, 10-14 years. The most commonly affected group was 0-5 years with 67 (39.41%) cases as shown in table 1.
- The sex-wise distribution is given in and table 2. In the present study, total males were 110(64.70%) and females were 60(35.29%) with M:F ratio of 1.8:3.
- The incidence of various solid malignant tumors observed is given in table 3. In the present study CNS malignancies (123 cases) was most common followed by soft tissue tumors (13 cases), lymphoma (10 cases), germ cell tumors (8 cases), renal tumors (6 cases), bone tumors (2 cases) and neuroblastoma (3 cases).
- Stratification of patients as per tumor types [4] is given in table 4. In CNS tumors most common tumor was ependymoma, while in germ cell tumors, teratoma (Mature cystic) was most common.

Table 1: Age wise distribution (Total case = 170)

Age in group	Total cases	Male	female
0-5	67(39.4%)	48	19
6-9	48(28.23%)	30	18
10-14	55(32.35%)	32	23

Table 2: Sex wise distribution

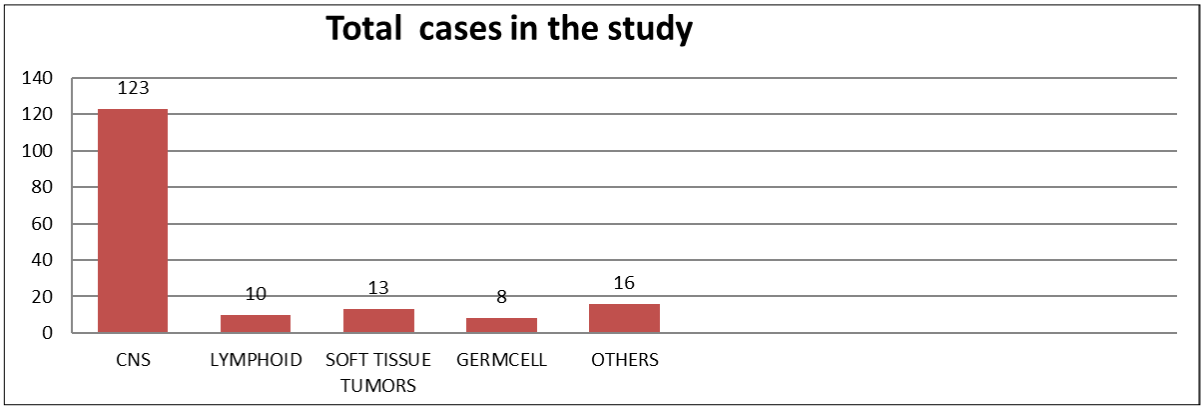
Total cases	170
Male	110
Female	60



Graph 1: Sex wise distribution

Table 3: Age wise Incidence of various Solid Malignant Tumors observed [4].

Diagnosis	0-5 years	6-9 years	10-14 years	Total	% Total
Cns	31	36	42	123	72.35
Lymphoid	1	5	5	10	5.9
Soft tissue	12	6	1	13	7.6
Germcell	10	0	0	8	4.7
Kidney	5	1	0	6	3.5
Neuroblastoma	3	0	0	3	1.8
Bone	1	0	1	2	1.2



Graph 2: Total cases in the study.

Stratification of patients as per tumor types C [1]

Table 4: CNS malignancies observed

Tumor Types CNS malignancy	No. of Cases	Male	Femali
Gliomas, glioneuronal, and neuronal tumors			
Low grade gliomas -Astrocytoma	17	9	8
Circumscribed astrocytic gliomas			
Filocytic astrocytoma	27	22	5
Reomorphic xanthoastrocytoma	2	2	-
Glioneuronal and neuronal tumors			
Ependymal tumors	53	40	13
myxopapillary ependymoma	1	1	-
Choroid plexus tumors			
Choroid plexus papilloma	2	2	-
Choroid plexus carcinoma	1	-	1
CNS embryonal tumors			
Medulloblastoma, histologically defined	16	9	7
Atypical teratoid/rhabdoid tumor	2	2	-
Pineal region tumors	2	-	2

Salient features of CNS malignancies

- **Ependymoma:** Ependymal rosettes with dense meshwork of fibrillary cytoplasmic processes. Tumor cell are rounded or spindled having granular chromatin and lack of nucleoli. Cells may contain invaginated cytoplasmic pseudo inclusions.
- **Pilocytic astrocytoma:** Biphasic cells consisting of compact fascicular and loose microcystic patterns. Cells have narrow, elliptical nuclei and long parallel process oriented in parallel. Rosenthal fibres (thick eosinophilic fibres) and eosinophilic granular bodies are characteristic of Pilocytic astrocytoma.
- **Medulloblatoma:** Packed sheets of primitive small undifferentiated cells with hyperchromatic, round or angulated nuclei with little or no definable cytoplasm with scanty stroma. Perivascular pseudorosettes are present.
- **Pleomorphic astrocytoma:** Pleomorphic cells with frequent nuclear inclusions, intracytoplasmic xanthomatous changes and spindle cells arranged in fascicular pattern. Reactive lymphoid infiltrates, eosinophilic granular bodies are seen.
- Choroid plexus papilloma show structure of the normal choroid plexus with fibrovascular core lined by a single layers of uniform cuboidal or columnar cells and almost epithelial appearance.
- Choroid plexus carcinoma-geographic foci of necrosis and hemorrhage.
- The Atypical teratoid/rhabdoid tumor (AT/RT). Rhabdoid cells have distinct cell borders, large and vesicular nuclei, macronucleoli and paranuclear cytoplasmic inclusions. The non-rhabdoid, large cells are mostly epithelioid elements in nests or sheets.

Table 5: Soft tissue tumors malignancies observed

Tumor Types Soft-Tissue Tumors	No. of cases	Male	Female
Fibroblastic and myofibroblastic tumors			
Low grade fibromyxoid sarcoma	1	1	-
Inflammatory myofibroblastic tumor	2	-	2
Fibrohistiocytic tumors	1	1	-
Skeletal muscle tumors			
Rhabdomyosarcoma family	7	3	4
Granular cell tumor	1	1	-
Tumors of uncertain differentiation			
Clear cell sarcoma of soft tissue	1	1	

Salient features of soft tissue tumors

- **Rhabdomyosarcoma:** varying degree of cellularity with alternating hypercellular areas and myxoid areas. Cell population consisted of mixture of undifferentiated, small, hyperchromatic round or spindle shaped cells and varying number of differentiated, strap or tadpole-shaped cells with eosinophilic cytoplasm (Rhabdomyoblasts).
- **Inflammatory myofibroblastic tumor:** Fascitis-like pattern, cellular spindle cell areas and hypocellular hyalinized zones. Lymphocytes and plasma cells are often intermixed.
- **Low-grade fibromyxoid sarcoma:** low cellularity with bland spindle-shaped cells deposited in variably myxoid and collagenous matrix with network of capillaries.
- **Clear Cell Sarcoma:** solid nests and fascicles of pale fusiform or cuboidal cells. Nucleoli are large and deeply basophilic. The tumor cells can also contain cytoplasmic melanin.

Table 6: Lymphoid neoplasm observed

Tumor Types Lymphoid neoplasms	No. of Cases	Male	Female
Mature B-cell neoplasms	2	1	1
Hodgkin lymphoma			
Nodular lymphocyte predominant	3	2	1
Histiocytic and dendritic cell neoplasms			
Langerhans cell histiocytosis	2	1	1
Atypical lymphoproliferative lesion	3	1	2

Salient features of lymphoid neoplasm

- **Non Hodgkin lymphoma:** diffuse and monomorphic pattern of proliferation with focal starry sky appearance with neoplastic cells having scanty cytoplasm and nucleus that has a round contour.
- **Hodgkin lymphoma showed Reed:** Sternberg cells in background of polymorphic reactive inflammatory cell population accompanied by fibrosis .Reed Sternberg cell is a large cell with abundant acidophilic or amphophilic, homogeneous cytoplasm, bilobed or

mutilobed nucleus and thick nuclear membrane. Round, prominent, highly acidophilic central nucleolus surrounded by a clear halo.

- **Langerhan cell histiocytosis:** sheet like accumulation of mainly dendritic cells with eosinophils, neutrophils, foamy histiocytes, giant cells, areas of fibrosis and fragmented bony trabeculae.
- **Atypical lymphoid proliferation:** lymphohistiocytic infiltrate, multinucleated giant cells and scattered foci of necrosis, perivascular lymphocytic infiltrate with occasional atypical cells.

Table 7: Germ cell Tumors observed

Tumor Types Germ cell tumors	No. of Cases	Male	Female
Nongerminomatous germ cell tumors			
Mature cystic teratoma	3	1	2
Extra-gonadal teratoma	1	1	-
Immature teratoma (Female gonadal)	2	1	1
Malignant mixed germ cell tumors	2	1	1

Salient features of Germ cell tumors

- Mixed germ cell tumors are composed of two or more of malignant germ cell histologic types.
- **Yolk sac tumor:** intermingling of epithelial and mesenchymal elements in a characteristic organized fashion. Perivascular Schiller-Duval bodies is the most distinctive feature.
- **Embryonal carcinoma:** large, epithelial appearing cells that resemble the early embryonic cells of the inner cell mass. The tumor cells are seen in solid, papillary or reticular patterns, forming many clefts and gland like structures.
- **Choriocarcinoma:** mixture of cytotrophoblast, syncytiotrophoblast and extravillous trophoblast in random fashion with areas of hemorrhage and necrosis.
- **Seminoma:** monotonous proliferation of large, uniform cells with central large nuclei and prominent nucleoli with clear or granular cytoplasm.

Table 8: Other malignancies observed

Tumor Types	No. of Cases	Male	Female
Wilms tumour	6	2	4
Neuroblastoma	3	3	-
Bone tumors	2	1	1
Mucoepidermoid carcinoma- Low grade	1	1	-
Mucinous Adenocarcinoma - signet ring cell type	1	-	1
Sinonasal teratocarcinosarcoma	1	-	1
Right adnexal mass with D/D clear cell carcinoma of ovary, yolksac tumor, metastatic RCC and serous carcinoma of ovary	1	-	1
Atypical Paraganglioma with neural features	1	-	1

Salient features of other malignancies

- **Triphasic wilms:** Edematous stroma, fibrovascular and granulation tissue, foamy histiocytes, areas of necrosis and unaffected differentiated elements include glomeruloid and tubular components, scattered inflammation, few scattered giant cells, areas of hemorrhage with hemosiderin laden macrophages.
- **Dedifferentiating Ganglioneuroblastoma:** mature to mildly dysmorphic ganglion cells dispersed as well as clustered against the schwannian background. Few tiny unencapsulated collections of malignant small round cells forming microscopic nests and scattered atypical mitoses.
- **PNET:** Solid sheets of cells separated by fibrous strands. Individual cells are small, round blue cells with indistinct cell outlines.
- In the present study cases were included in miscellaneous category, the cases included under this category were, Mucoepidermoid carcinoma- Low grade a case of Mucinous Adenocarcinoma - signet ring cell type invading into muscularis propria. TNM stage - T2NXMx, Sinonasal Teratocarcinosarcoma, right adnexal mass in 0 year old female with diagnostic possibilties of 1) Clear cell carcinoma of ovary. 2) Yolk sac tumor. 3) Metastatic renal cell carcinoma. 4) Serous carcinoma of ovary and Atypical Paraganglioma with neural features.

Discussion

In present study 170 cases of pediatric solid malignancies in the age group of 0- 14 were studied. The information is useful in showing patterns of childhood malignancies in our region. Distribution of various malignant tumors encountered in the present study are compared with similar studies conducted in different parts of India as well as other country. Table 9.

Table 9: Incidence of various malignancies observed by various workers

Histological type	Sharma S 2004 [10]	Gvandana 2015 [9]	Harshmohan 2014 [11]	Sweden study Ljungman *et al*. [12]	Present study
CNS	-	23.4%	23.4%	-	72.35%
Lymphoma	21.4%	7.27%	7.27%	21.9%	5.9%
Soft Tissue	10.3%		17.27%	14.5%	7.6%
Neuroblastoma	3.8%	11.42%	0.91%	14.3%	1.8%
Kidney	19.4%	25.71%	-	19.8%	3.53%
Germcell Tumors	8.4%	8.57%	3.64%	8.44%	4.7%
Bone	9.7%	-	32.73%	9.4%	1.2%

- In the present study most common malignancies observed were CNS malignancies (72.35%) and is comparable with the study of G vandana [9]and Harshmohan [12], possible reason can be of the well-established Pediatric surgery and Neurosurgery Department in our institution.
- The data in table 9 reflects the wide geographical variation in cancer incidence. The advancement of the research in pathogenesis and immunohistochemical markers which may be attributed to possible differences in genetic predisposition.
- The most commonly affected age group was 0-5 years with 67 (39.41%) cases are comparable with studies of Dawani [18] Jussawala [19] table 10.Age also has strong prognostic relevance in certain malignancy. It has observed that, infants with neuroblastoma seemed to have better prognosis than older children even after minimal therapy [9]. However, age <1 year at diagnosis has been associated with worse prognosis in rhabdomyosarcoma (RMS). The earlier age group showed prevalence of embryonal tumors whereas older ages suffered more from astrocytic tumors [9].
- The mean age of presentation was 7.74 years. The M:F ratio was 1.8:3.

Table 10: Age distribution observed by various workers:

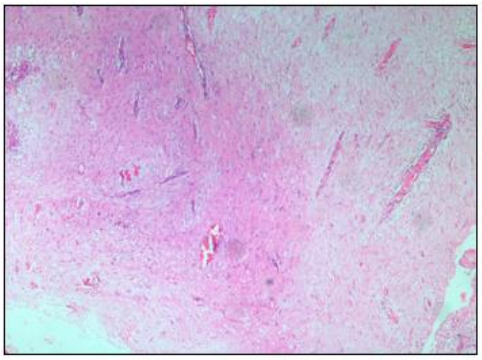
Sr. No.	Studies	0-5	6-9	10-14
1.	Dawani [18]	42%	29%	29%
2.	Jussawala[19]	47.2%	40.9%	11.9%
3.	Present study	39.41%	28.23%	32.35%

- Male predominance is a salient feature of many childhood tumors as was in our study and are comparable with studies of G vandana [9] Das S [15] CT Nagaraja[16] Yeole BB [17] table 12. The observed incidence disparities may be due to sex differences in exposure, genetics or immune response [15].

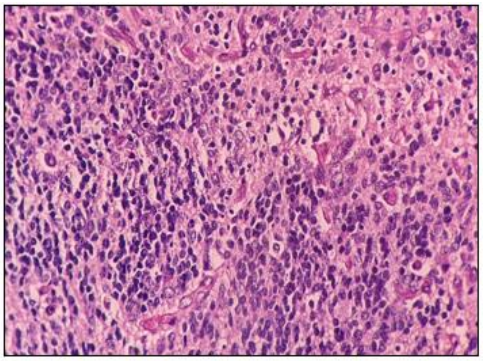
Table 11: Sex ratio observed by various workers

Sr. No.	Studies	Male	Female	Ratio M:F
1.	Gite Vandana [9]	24	11	2.2:1
2.	Das S [15]	127	65	1.95:1
3.	CT Nagaraja [16]	40	26	1.53:1
4.	Yeole BB [17]	814	516	1.58:1
5.	Present study	110	60	1.8:1

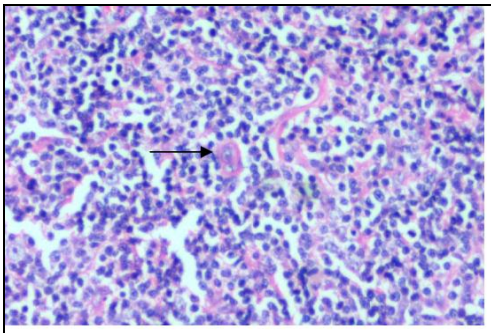
Microscopic appearance of lesions



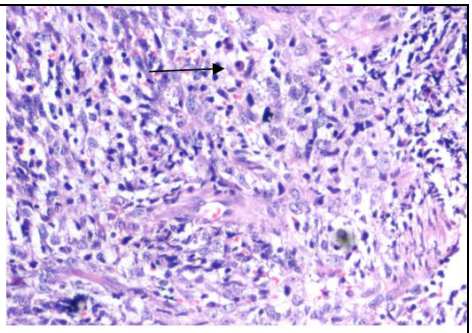
Pilocytic Astrocytoma: H & E (10X) Biphasic cells consisting of compact fascicular and loose microcystic pattern with eosinophilic granular bodies.



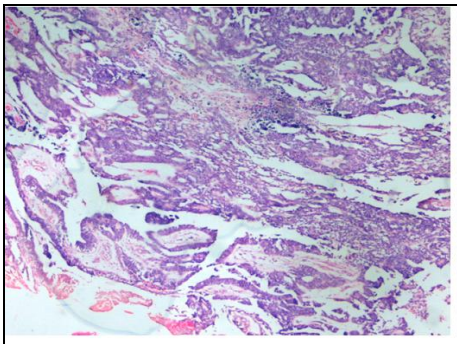
Medulloblastoma: H & E (10X) Sheets of primitive small undifferentiated cells having hyperchromatic nuclei and little or no definable cytoplasm with scant stroma.



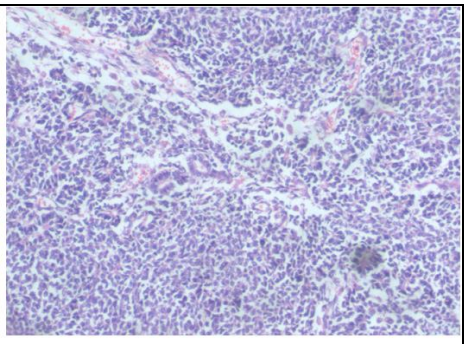
Hodgkin's Lymphoma: H & E (40X) Reed Sternberg cell (arrow) in a background of polymorphic inflammatory cell population with fibrosis.



Rhabdomyosarcoma: H & E (40X) Mixed cell population of undifferentiated small hyperchromatic round and spindle shaped cells with varying number of rhabdomyoblast (arrow).



Yolk Sac Tumor: H & E (20X) Mixed epithelial and mesenchymal elements with perivascular Schiller Duval bodies.



Wilm's Tumor: H & E (20X) Differentiated elements including glomeruloid and tubular epithelial components with scattered inflammation, areas of haemorrhage

Conclusion

This study highlights the importance of histological examination of resected or biopsied tumors. Even though there are great innovations in ancillary studies, the simple H&E stained slides continue to exist as an invaluable means to diagnose and classify CNS tumors. The diagnostic shift from morphology to immunohistochemical and molecular analyses is driven by the need for an unbiased classification to optimally serve our patients. The likelihood of a given type of tumor being present in a particular age or sex group or particular site may heighten the index of suspicion which ultimately influences etiology, biology, natural history, relative incidence, distribution frequency and response to therapy for both improved survival chances and minimizing risks for long-term sequelae.

Source of funding: Self

Ethical clearance: All procedures performed were in accordance with the ethical standards of the institution.

Conflicts of interest: Nil

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How to Cite This Article
Vaishnavi P, D Hemina, G Hansa. Histopathological study of pediatric solid malignant tumors in a tertiary care hospital. International Journal of Clinical and Diagnostic Pathology. 2022;5(4):74-79.