

Research

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The Spectrum of Malignant Solid Childhood Tumors in the Age Group of 0-12 Years

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ABSTRACT

Objective: To document general baseline data on the patterns of childhood malignant tumors in a surgical pathology department.

Design, Setting and Participants: This is a retrospective analysis of 35 cases of pediatric tumors in surgical pathology department of tertiary care hospital excluding neurosurgery, cardiothoracic and haemato-lymphoid malignancies. (Age group 0-12 years) encountered over a period of 5 years.

Results: 35 children were diagnosed with malignant tumors. The commonest tumor was wilms tumor (9 out of 35 cases) followed by neuroblastoma (4 out of 35 cases). The common age of presentation was 1-5 years with male predominance. In the renal tumors only wilms tumors (9 cases) was seen, with classical triphasic tumors were more common. The mean age of presentation was 3 year with commonest age group of presentation (8 cases out of 9) in the age group 1-5 years. Three of them had showed unfavorable histology. In the adrenal gland, adrenal medullary tumors were more common than adrenal cortex with neuroblastoma (4 of 6 cases) as common individual tumor. Immunohistochemistry performed on 10 of 11 round cell tumors revealed five cases of lymphoma, three cases of Rhabdomyosarcoma (RMS) & two cases of Ewing sarcoma-primitive neuroectodermal tumor (EWS/PNET).

Conclusion: Histological type is important for understanding etiology and progression of disease. 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 and ultimately influences etiology, biology, and natural history, relative incidence and distribution frequency, clinical presentation and manifestations, and response to therapy and outcome.

KEYWORDS: Neuroblastoma; Rhabdomyosarcoma; EWS/PNET.

ABBREVIATIONS: hCG: human Chorionic Gonadotropin; AFP: Alpha fetoprotein; LDH: Lactate dehydrogenase; NHL: Non-Hodgkin Lymphoma; RMS: Rhabdomyosarcoma; ACC: Adrenocortical carcinoma; PHPV: Persistent Hyperplastic Primary Vitreous.

INTRODUCTION

Incidence of childhood malignant tumors is on the rise all over the globe, though it is a small fraction of the overall global tumor burden. Yet for children and their families it can be deeply distressing. Although childhood malignant tumors occur infrequently, they present a challenging diagnostic and therapeutic problem. Unfamiliarity with these conditions may lead to the erroneous diagnosis and unnecessarily aggressive therapy.

Malignancy is the second most common cause of childhood mortality in the developed world, accounting for 12.3% of all childhood deaths in USA.¹ Although major cause of childhood mortality in the developing world is still malnutrition and infections, childhood malignant tumors are also rising in number. About 1/650 children develops malignancy before their 15th birthday.² Malignancies accounts for the major cause of death in Indian children next only to infection and malnutrition. Approximately 35,000 to 40,000 children develop malignancies

each year in India.²

Thus, the appropriate management of pediatric tumors requires detailed clinical history, tumor site, and precise histopathological diagnosis, accurate grading & staging wherever possible along with other clinical investigations. Histological type is important for understanding etiology and progression of disease. No histological diagnosis can be accurate without a clinico-radio-pathological correlation.

MATERIALS AND METHODS

This was a retrospective analysis of 35 cases of pediatric tumors in surgical pathology department excluding neurosurgery, cardiothoracic and haemato-lymphoid malignancies. (Age group 0-12 years) encountered over a period of 5 years: January 2004-December 2008. Surgical specimens and biopsy tissues received were fixed overnight in 10% buffered formalin and submitted for processing. Paraffin sections were cut at 4-6 microns thickness and routine H & E staining was performed. All cases were re-evaluated histologically on sections from routinely processed formalin fixed, paraffin embedded blocks. Special stains & Immunohistochemistry were studied wherever necessary. The clinical, radiological and therapeutic data was obtained from patients case paper records. Pattern of childhood malignancies was studied with a focus on tumor incidence, age and sex distribution, environmental and other etiological factors, demographic pattern, and histological type.

RESULTS

A total of 3149 pediatric surgical specimen presented over a five years. Of this, 35 were diagnosed with malignant tumors. Average incidence of malignant pediatric tumors was 1.11%. The commonest tumor was wilms tumor (9 out of 35 cases) followed by neuroblastoma (4 out of 35 cases). The common age of presentation was 1-5 years with male predominance. In the renal tumors only wilms tumors (9 cases) was seen, with classical triphasic tumors were more common. The mean age of presentation was 3 year with commonest age group of presentation (8 cases out of 9) in the age group 1-5 years. Three of them had showed unfavorable histology. In the adrenal gland, adrenal medullary tumors were more common than adrenal cortex with neuroblastoma (4 of 6 cases) as common individual tumor. Among the gonadal germ cell tumors, there were noted one immature teratoma, two yolk sac tumors of ovary & one yolk sac tumor in testis. Immunohistochemistry performed on 10 of 11 round cell tumor revealed five cases of lymphoma, three cases of rhabdomyosarcoma & two cases of EWS/PNET.

DISCUSSION

In literature, differences have been demonstrated in the incidence rates of pediatric malignant tumors as they are studied by anatomic site, age, race or gender. They are also studied in reference to various parameters such as total pediatric tumor against total pediatric hospital admissions or total autopsy study

or total surgical pathology sample received. The present study comprises of 35 cases (1.11%) of childhood malignant tumors from a total of 3149 pediatric surgical specimens received over a period of 5 years. It is difficult to compare incidence data because of the difficulties associated with retrieving demographic data for previously studied pediatric populations.

Most of the childhood malignant tumors occur below the age of eight years, although wide age variability exists in children.² In the present study, 12 years was considered as the pediatric age with infancy as a separate age group. Neuroblastoma, Wilms tumor, retinoblastoma and hepatoblastoma were strikingly more in children younger than 5 years of age, similar to that observed by Kusumakumary P, et al.³ However, round cell tumors, non-neuroblastic adrenal tumors presented commonly in the age group of 5-10 years. Age also has strong prognostic relevance in certain tumor. It has observed that, infants with neuroblastoma seemed to have better prognosis than older children even after minimal therapy.⁴ However, the age <1 year at diagnosis has been associated with a worse prognosis in rhabdomyosarcoma (RMS).⁵ Male predominance is a salient feature of many childhood tumors.² There is higher incidence in males with male to female ratio of 2.2:1. Male preponderance was seen in wilms tumor, round cell tumor. There were equal incidence of Neuroblastic tumors in males & females.

Childhood malignant tumors account for no more than 2% of all cancers. The tumors encountered by Sebastian, et al.⁶ were lymphomas 44.3%, Wilms tumor 20.1%, sarcomas 11.5%, neuroblastoma 8.6%, retinoblastoma 8.0%, teratomas 4.6% and hepatoma 2.9%. In the present study, wilms tumor with 9 cases (25.71%) was the largest group.

All pediatric renal tumors were Wilms tumor i.e. 100% as compared to the 78.4% by Louisa Paul, et al.⁷ This difference may be due to small sample size in the present study. All the cases in this study presented with abdominal mass. Eight out of 09 cases were presented in an age group 1-5 years & 01 case was seen in an age group 0-1 year, which was comparable to the study done by Louisa Paul, et al.⁷ The median age of presentation was 3 years. Thus, the age distribution was consistent with other studies.⁷⁻⁹ Wilms tumor presenting in infancy when treated appropriately has a good outcome. Age 4 years at first diagnosis is clearly an adverse prognostic factor probably that due to adverse biologic features. There were seven cases in males & two in females giving a ratio of male to female ratio of 3.5:1. This was slightly on higher side as compared to study done by Louisa Paul, et al.⁷ Patel A. A., et al¹⁰ in their study of 11 infantile Wilms tumor found the male to female ratio was 2.3:1. Husain A. N., et al.⁸ found Wilms tumor slightly more common in girls in whom it tends to present at an older age.

The mean tumor size in present study was 8 cm with a range of 4cm to 15 cm. One of the poles of kidney was commonly affected. This was in accordance to the study done in the literature.⁶ Eight cases (88.89%) were classical (Triphasic) composed of epithelial, blastemal, and stromal elements and one

case was monophasic type with predominantly epithelial component. Four other types of renal tumors can occur in childhood with sufficient frequency are mesoblastic nephroma, clear cell sarcoma of the kidney, rhabdoid tumor, and renal cell carcinoma. Congenital mesoblastic nephroma is the most common renal tumor in infants.⁸

It has observed that, infants with neuroblastoma seemed to have better prognosis than older children even after minimal therapy.¹² About 37% are diagnosed as infants, and 90% are younger than 5 years at diagnosis, with a median age at diagnosis of 19 months.¹¹ In the present study, four of neuroblastoma cases were presented at the age of 11 months, 18 months, 3 years & 5 years with male & female ratio of 1:1. In several large series, no overall sex predominance has been reported.¹¹ All were presented with suprarenal or retroperitoneal mass & pain. Uncommon manifestations of NB related to unusual clinical behavior or to paraneoplastic syndromes were not seen in any case. Pathologically, tumor cells forming the typical Homer-Wright rosettes arranged around the central fibrillary material without a central lumen or canal also seen. Mitotic activity was low in two of surgically resected neuroblastic tumors and absent in two of biopsy material. Calcification was noticed in all cases. The bone marrow biopsy record was not available in any case, which is also important in the monitoring of the disease activity.

Some neuroblastomas have substantial internal morphologic variability about the degree of neuroblastic differentiation, ganglion cell maturation and Schwannian stroma. Differentiation in neuroblastic cells is recognized as neuropil formation and the acquisition of gangliocytic features. The phenomenon of differentiation has been codified by use of the term Ganglioneuroblastoma to denote intermediate differentiation and Ganglioneuroma to denote the fully mature neuroblastic neoplasm. One case of ganglioneuroblastoma at the age of 4 years in females was documented presenting as suprarenal mass.

Adrenocortical carcinoma (ACC) are rare tumors that have a bimodal distribution, the first peak is in children less than five years and the second around the fifth decade.¹³ A single case of Adrenocortical carcinoma at an age of 7 years in a female child, grossly have shown size of 15*12 cm, weight 650 gm, nodular mass with solid, cystic & necrotic areas. Microscopically the growth pattern was diffuse sheets of tumor cells with bright pink cytoplasm & broad mitotically active pleomorphic cells separated by broad fibrous bands and capsular invasion. Cagle, et al.⁸ specifically studied the adrenal cortical neoplasms in children; they found that only size (expressed as weight) was a reliable predictor of malignancy, with a weight greater than 500 g indicative of a carcinoma.⁸ The macroscopic features, presence or absence of necrosis and microscopic features, such as broad fibrous bands in the tumor, increased mitotic activity, capsular invasion, and a diffuse growth pattern helped to differentiate between adenoma & carcinoma.

The usual age at diagnosis of retinoblastoma is between 12 and 24 months, with an average age of 18 months.⁸ Children

diagnosed in first 3 months are usually seen because of a family history of retinoblastoma.¹⁴ There is no significant sex or race predilection, and 20 to 35% cases are bilateral.⁸ In present study, there were three cases of retinoblastoma, all seen in the age group of 1-5 years with male to female ratio as 2:1. All three cases presented with white reflex in the pupil i.e. leukocoria. Enucleation was done in all cases. Common pattern of presentation was endophytic growth. Microscopically they had shown sheets of round cells with hyperchromatic nuclei; arise from retina & Homer Wright rosettes and necrosis. Optic nerve was free of tumor in all three cases. Children with retinoblastoma may have other congenital abnormalities such as 13q-deletion syndrome, other trisomies, Persistent Hyperplastic Primary Vitreous (PHPV), and congenital cataracts.

Hepatoblastoma accounts for 1.5% of all malignancies in children younger than 5 years of age and is the most common liver cancer in children. There was one case of hepatoblastoma located in the right lobe of liver in a 7-month-old male child. Nearly 90% of hepatoblastomas are seen in the first 5 years of life; with 68% discovered in the first 2 years and 4% present at the time of birth.⁸ A striking presentation of hepatoblastoma is seen in children (particularly young boys) whose tumors produce human Chorionic Gonadotropin (hCG), leading to precocious puberty with genital enlargement, the appearance of pubic hair and a deepening voice. Clinical presentation was of an abdominal mass with hepatomegaly. Serum Alpha fetoprotein (AFP) & Lactate dehydrogenase (LDH) levels were raised with normal liver function tests. Grossly it was solid, solitary, well circumscribed with a variegated appearance with areas of haemorrhage & necrosis. On histology, the tumor cells seen were of fetal & embryonal type cells arranged in lobules, sheets, nests separated by fibrous septae with capsular invasion.

The term "round-cell tumor" describes a group of highly aggressive malignant tumors of childhood with diverse histogenesis. These are composed of relatively small and monotonous undifferentiated cells with round nuclei & high nuclear to cytoplasmic ratios. A clear understanding of their clinicopathologic features usually allows for a confident diagnosis, especially if immunohistochemistry for individual protein markers is used.

In the present study, 11 cases of round cell tumors were documented. These were seen predominantly in males. The common age group was 5-10 years and most often were located in the head neck region. Their clinical presentations often overlap, thus making a definitive diagnosis a problem. Based on the immunohistochemistry, there were five cases of lymphoma, three cases of rhabdomyosarcoma & two cases of PNET/Ewing's sarcoma. Non-Hodgkin lymphoma represents a multitude of discrete types of lymphoid neoplasia, each with its own molecular pathogenesis, distinctive pattern of clinical behavior, and therapeutic response. In the present study, out of five lymphoma cases, there were three cases of Burkitts type NHL, and one case each of B & T cell NHL. Burkitts type Non-Hodgkin lymphoma (NHL) presented at the age of 7 months, 4 years & 9 years. B cell & T cell NHL were at the age of 2.5 & 11 years respectively.

In contrast to equal incidence by Louic P, et al.⁸ all in the present study were in the males. Three cases were located intra abdominally. Most of them were presented with fever, lump, and weight loss. LCA positivity is seen in all cases. Burkitts & B cell NHL had shown CD 20 & CD 10 positivity. T cell NHL had shown CD 3 Positivity (Table 1).

| Group | Number of Malignant tumor | % |
|--|---------------------------|---------|
| I) Leukemias | Excluded | - |
| II) Lymphomas and Reticuloendothelial Neoplasms | Excluded | - |
| III) CNS and Miscellaneous Intracranial and Intraspinial Neoplasms | Excluded | - |
| IV) Sympathetic Nervous System Tumors | 6 | 17.15% |
| V) Retinoblastoma | 3 | 08.57% |
| VI) Renal Tumors | 9 | 25.71% |
| VII) Hepatic Tumors | 1 | 02.86% |
| VIII) Malignant Bone Tumors | - | - |
| IX) Soft-Tissue Sarcomas | - | - |
| X) Germ-Cell, Trophoblastic and other Gonadal Neoplasms | 3 | 08.57% |
| XI) Carcinomas and other Malignant Epithelial Neoplasms | 2 | 05.71% |
| XII) Other and Unspecified Malignant Neoplasms | 11 (Round cell tumors) | 31.43% |
| Total | 35 | 100.00% |

Table 1: Paediatric malignant tumor according to international Classification of Childhood Cancer (ICCC).

Rhabdomyosarcoma is the most common soft tissue sarcoma in the childhood, accounting for about 50% of childhood soft tissue. Rhabdomyosarcomas are generally immunoreactive for vimentin, myogenic regulatory protein, myoD1, myogenin, muscle-specific actin, desmin, and myoglobin. A minority of cases express smooth muscle actin, and aberrant expression. In the present study, all three cases presented at the age of 6.5, 7 & 8 years old male child respectively. The most frequent sites of origin are the head and neck, genitourinary tract and pelvis, and extremities.⁸ The location of the primary tumor or its metastases determines the clinical presentation. In the present study, all three case were in head neck & face region only.

Ewing sarcoma-primitive neuroectodermal tumor is the second most common primary osseous or soft tissue malignancy in the first two decades of life, with one EWS-PNET for every three osteosarcomas. A biopsy specimen of a poorly marginated medullary lesion with permeative bone destruction and cortical loss, a soft tissue mass in the pelvis, or a paravertebral mass with an adjacent vertebral or rib lesion is the usual introduction of EWS-PNET to the pathologist. In the present study, two cases of EWS-PNET had been diagnosed after immunohistochemistry. They presented in an 11 years old male & 8 years old female located in the intrathoracic region & nasal maxillary sinus respec-

tively. Microscopically they showed monotonous monolayered round cell neoplasm with non overlapping polygonal cells that have a distinct cell membrane, a uniform round to oval nucleus with finely dispersed granular chromatin, a small nucleolus, and clear to finely vacuolated cytoplasm. Both cases were Mic2 positive but negative for LCA, CD2, CD3, CD10, Myoglobin, MYO D1, Neuron-specific enolase (NSE), Cytokeratin (CK), Epithelial Membrane (EMA), chromogranin & synaptophysin.

Other common round cell tumors in childhood are desmoplastic small round blue cell tumor, Mesothelioma, Neuroblastoma & Wilms tumor. Desmoplastic small round cell tumor has predilection for the abdomen and retroperitoneum. Desmoplastic small round cell tumor is considered a member of the PNET-EWS family of tumors but is much less common than EWS and PNET. Desmoplastic small round cell tumor exhibits a combination of mesenchymal, epithelial, and neural features. The immunophenotype includes reactivity for keratin, epithelial membrane antigen, vimentin, desmin, neuron-specific enolase, EWS-WT1 chimeric protein, and CD99. Rarely, desmoplastic small round cell tumor displays immunoreactivity for actin, other neural markers, and p53.⁸

Malignant germ cell tumors in the ovaries of very young children are exceedingly rare. In the present study one case was of immature teratoma, two cases of yolk sac tumor in ovary and one case of yolk sac tumor in the testis was documented. All three cases of the ovary presented at the age of 11 years & showed elevated levels of AFP. Yolk sac tumors are the second most common histological subtype (22%) of malignant ovarian germ cell tumor in children. Yolk sac tumors are the most common testicular germ cell tumor in childhood, representing in excess of 60% of cases and almost 50% of all testicular tumors in children.⁸ An asymptomatic scrotal mass in a child younger than 3 years of age are the common presentation. The histology and cytology of yolk sac tumors vary widely, often causing difficulty in diagnosis. The prototypic Schiller-Duval bodies of endodermal sinus tumors are present in 50-75% of tumors.⁸ Yolk sac tumors are commonly associated with highly elevated serum AFP levels, which may be monitored clinically for recurrence and/or metastasis. In the present study, two of the yolk sac tumor was located at ovary & one at testis. All three had showed elevated levels of AFP. Both ovarian yolk sac tumors presented at the age of 11 years & one case of testicular yolk sac tumor at the age of 5 years. Grossly they have solid, yellow appearance. Microscopically polygonal tumor cells in reticular, trabecular & papillary pattern seen with Schiller-Duval bodies. Microcystic change is seen in one ovarian yolk sac tumor (Tables 2 and 3).

All tumors of the bladder and urethra are rare in children. In the present study, one case of squamous cell carcinoma at the age of 10 years was documented and no any predisposing factor was elicited. In contrast to adults, most pediatric bladder carcinomas are low grade, superficial, and have a good prognosis following transurethral resection. Rare cases of, leiomyosarcoma, and secondary involvement of leukemia, lymphoma, and

| | Tumor | 0-1yr | 1-5 yrs | 5-10 yrs | 10-12 yrs | Total |
|----------------------|--------------------------|-------|---------|----------|-----------|-------|
| Genitourinary system | Immature teratoma | | | | 1 | 1 |
| | Yolk sac tumour | | 1 | | 2 | 3 |
| | Wilms tumour | 1 | 8 | | | 9 |
| | Bladder carcinoma | | | 1 | | 1 |
| Round cell tumors | | 1 | 2 | 6 | 2 | 11 |
| Adrenal | Adrenocortical carcinoma | | | 1 | | 1 |
| | Ganglioneuroblastoma | | 1 | | | 1 |
| | Neuroblastoma | 1 | 3 | | | 4 |
| Eye | Retinoblastoma | | 3 | | | 3 |
| Liver | Hepatoblastoma | 1 | | | | 1 |
| | Total | 4 | 18 | 8 | 5 | 35 |

Wilms tumors & neuroblastoma were commonly presented in age group 1-5 years & round cell tumor in 5-10 years.

Table 2: Age distribution of individual tumor.

| | | Male (M) | Female (F) | Total | M: F |
|----------------------|--------------------------|----------|------------|-------|-------|
| Genitourinary system | Wilms tumour | 7 | 2 | 9 | 3.5:1 |
| | Bladder carcinoma | 1 | | 1 | 1(M) |
| | Immature teratoma | | 1 | 1 | 1(F) |
| | Yolk sac tumour | 1 | 2 | 3 | 1:02 |
| Round cell tumor | | 9 | 2 | 11 | 4.5:1 |
| Adrenal | Adrenocortical carcinoma | | 1 | 1 | 1(F) |
| | Ganglio-neuroblastoma | 1 | | 1 | 1(M) |
| | Neuroblastoma | 2 | 2 | 4 | 1:1 |
| Eye | Retinoblastoma | 2 | 1 | 3 | 2:1 |
| Liver | Hepatoblastoma | 1 | | 1 | 1(M) |
| | Total | 24 | 11 | 35 | 2.2:1 |

Table 3: Gender distribution of individual tumor.

Wilms tumor has been reported.⁸

So, to conclude, histological type is important for understanding etiology and progression of disease. 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 and ultimately influences etiology, biology, and natural history, relative incidence and distribution frequency, clinical presentation and manifestations, and response to therapy and outcome.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

CONSENT

The patient has provided written permission for publication of the case details.

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