

# Histopathological study of childhood tumors of the urogenital system



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## ABSTRACT

**Background:** Malignancies form one of the important causes of pediatric morbidity as well as mortality. These malignancies are increasingly becoming more important causes of pediatric mortality as deaths from other causes such as infections, malnutrition, and heart diseases are decreasing due to advances in field of pediatric medicine. Urogenital tumors form one of the important causes of pediatric urology consultations. This study was done to describe the spectrum and clinicopathologic features of childhood tumors of the urogenital tract in our institution. **Aims and Objectives:** The aims of this study were as follows: (1) To study the histopathology of childhood tumors of the urogenital system. (2) To describe the clinical, gross, and microscopic features of these tumors. **Materials and Methods:** This was a retrospective study conducted in the Department of Pathology of Christian Medical College, Vellore, in which children below 18 years of age, in whom biopsies or resections of tumors of the urogenital system was done, were included on the basis of a predefined inclusion and exclusion criteria. Slides of all such specimens were retrieved from the archives of General Pathology. The clinical features were recorded from cases papers. Microscopic and immunohistochemistry findings were studied. Data analysis was done using SPSS 16.0. Descriptive data were reported and compared. Categorical variables were reported using frequency and percentage. Continuous variables were reported using mean  $\pm$  standard deviation or median (interquartile range) as appropriate. **Results:** In our study of 100 pediatric patients with urogenital tumors, there were 55 boys (55%) and 45 girls (45%) amongst the studied cases with a M: F ratio of 1:0.81. The most common type of urogenital neoplasm in pediatric age group was found to be Wilms tumor which was seen in 55 (55%) patients. The other common histopathological findings were mature cystic teratoma (13%), mixed germ cell tumor (7%), yolk sac tumor (6%), and rhabdomyosarcoma (6%). Sertoli cell tumor, Sertoli-Leydig cell tumor, and clear cell renal carcinoma were less common and were seen in one patient (1%) each. **Conclusion:** Urogenital tumors in pediatric age groups form one of the important causes for pediatric urology consultation. In our study Wilms tumor was most common urogenital tumors followed by mature cystic teratoma, mixed germ cell tumor, yolk sac tumor, rhabdomyosarcoma, and immature teratoma.

**Key words:** Histopathology; Immunohistochemistry; Pediatric urogenital tumors; Wilms tumor

## INTRODUCTION

Cancers are an important cause of morbidity and mortality in children worldwide. Common causes of death in children below the age of five are perinatal disorders, congenital malformations, infections, and malnutrition; with advances in health care practice, deaths due to malnutrition and

infection have almost halved (91/1000–43/1000 live births) from 1990 to 2015.<sup>1,2</sup>

A report of 25 population-based cancer registries of India which was released in 2013 showed that age-adjusted cancer incidence rates ranged from 18.6 to 159.6/million for boys and 11.3–112.4/million for girls. According to this report,

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leukemias were the most common malignancies in both boys and girls. This data was based on children (0–14 years).<sup>3,4</sup>

Childhood cancers such as retinoblastoma and Wilms tumor may be familial. Ataxia telangiectasia and disorders such as Li Fraumeni, Beckwith Wiedemann, and multiple endocrine neoplasia (MEN) syndromes are also associated with childhood cancer. After hematological malignancies common childhood cancers include CNS tumors, lymphomas, neuroblastomas, soft-tissue sarcomas, Wilms tumors, germ cell tumors, and bone tumors.<sup>5</sup>

The childhood genitourinary tumors can be further divided into tumors of kidneys such as Wilms tumor, Ewing's sarcoma, primitive Peripheral neuroectodermal tumor (PNET), mesoblastic nephroma, clear cell sarcoma, Rhabdoid tumor, lymphoma, and neurogenic tumors. Out of renal tumors, the most common renal neoplasm in children is Wilms tumor. The other less common renal tumors include mesoblastic nephroma, clear cell sarcoma, and rhabdoid tumors. The other less common renal tumors include lymphoma and neurogenic tumors. The other category of urogenital tumors which primarily involves bladder, urethra, and ureters consist of tumors such as rhabdomyosarcoma, hemangioma, neurofibroma, leiomyoma, paraganglioma, and transitional cell carcinoma.<sup>6</sup>

The clinical features of these urogenital tumors vary depending on the pathology and site of involvement. Wilms tumor typically present as asymptomatic abdominal mass. Sometimes other clinical features which may be present include malaise, pain, and hematuria. Similarly, congenital mesoblastic nephroma may present with hematuria, childhood hypertension, hypercalcemia and elevated renin levels. Some rare tumors such as clear cell sarcoma of kidney may present with bone metastasis.<sup>7</sup> More aggressive tumors of kidneys such as rhabdoid tumor usually carry a bad prognosis, and in most of the cases, death occurs within 12 months of diagnosis. Moreover, these tumors are also associated with systemic manifestations such as paraneoplastic syndrome causing disturbances in calcium metabolism particularly hypercalcemia. Rare renal tumors in pediatric age group include neuroblastoma, Ewing's sarcoma or primitive peripheral neuroectodermal tumor (PNET), synovial sarcoma, renal cell carcinoma, and lymphomas.<sup>8</sup> The other tumors which, generally, involve other parts of genitourinary system include transitional cell carcinoma, leiomyoma, neurofibroma, hemangioma, and paraganglioma arising from urinary bladder. In girls teratomas, dysgerminoma, endodermal sinus tumor, and germ cell tumors can be seen.<sup>9</sup>

The diagnosis of these tumors usually requires a careful history and through clinical examination. Imaging

techniques such as ultrasound, computerized tomography, and magnetic resonance imaging play a crucial role in confirmation of diagnosis. Immunohistochemistry also plays a key role in the diagnosis. Histopathological confirmation is the most crucial factor in deciding further management plan in these cases.<sup>10</sup>

This study was done to describe the spectrum and clinicopathologic features of childhood tumors of the urogenital tract in our institution.

### Aims and Objectives

The objectives of this study were as follows:

1. To study the histopathology of childhood tumors of the urogenital system.
2. To describe the clinical, gross, and microscopic features of these tumors.

## MATERIALS AND METHODS

This was a retrospective study conducted in the department of Pathology of Christian Medical College, Vellore, in which children below 18 years of age, in whom biopsies or resections of tumors of the urogenital system were done, were included on the basis of a predefined inclusion and exclusion criteria. Slides of all such specimens were retrieved from the archives of General Pathology.

A total of 100 specimens from children with urogenital tumors were included in this study on the basis of a predefined inclusion and exclusion criteria. Keeping power ( $1-\beta$  error) at 80% and confidence interval ( $1-\alpha$  error) at 95%, the minimum sample size required in each group was 80 patients; therefore, we included 100 (more than minimum required number of cases) specimens in this study.

The demographic as well as clinical details were obtained from case papers. The demographic details such as age and gender were noted. History as well as clinical features were noted from case papers. Family history of any such urogenital tumors in any other family members was also looked into and if there was any such family history as present, then it was noted down. Details of blood investigations, presenting complaints, site and laterality, size of tumor, stage, as well as extent of spread of the tumor were noted. Imaging findings such as extension to the local area and adjacent tissue and presence of metastasis were also reviewed and noted. The histological appearance of the tumors was described along with the grade of the tumor, immunohistochemical findings, extent of invasion, and pathological stage, whenever possible. On histopathological examination, findings such as capsular

invasion, pattern of arrangement, nuclear features, invasion, and histopathological diagnosis were reviewed. Results of immunohistochemical studies if available were also recorded.

Data entry was done using Epidata/MS Excel. Data analysis was done using SPSS 16.0. Descriptive data were reported and compared. Categorical variables were reported using frequency and percentage. Continuous variables were reported using mean $\pm$ SD or median (interquartile range) as appropriate. For statistical purposes,  $P < 0.05$  was taken as statistically significant.

#### Inclusion criteria

All tumors of the urogenital tract seen in children aged 0–18 years of age were included in the study.

#### Exclusion criteria

Unavailability of slides or poor-quality slides and the paraffin blocks of which could not be retrieved for re-cutting were excluded from the study.

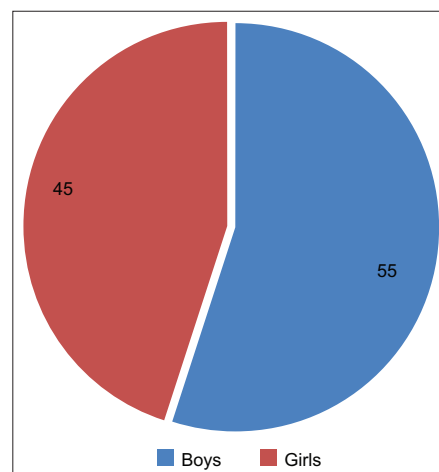
## RESULTS

There were 100 children with tumors of the urogenital system who fulfilled the inclusion criteria for this study. The analysis of gender distribution of the studied cases showed that there was a slight male preponderance in cases of urogenital tumors in pediatric age group. There were 55 boys (55%) and 45 girls (45%) among the studied cases with a M: F ratio of 1:0.81 (Figure 1).

The analysis of histopathology reports of the studied specimens showed that the most common type of urogenital neoplasm in pediatric age group was found to be Wilms tumor which was seen in 55 (55%) patients. The other common histopathological findings were mature cystic teratoma (13%), mixed germ cell tumor (7%), yolk sac tumor (6%), and rhabdomyosarcoma (6%). Sertoli cell tumor, Sertoli-Leydig cell tumor, and clear cell renal carcinoma were less common and were seen in one patient (1%) each (Table 1).

The analysis of the tumors on the basis of location showed that kidney (55%) was the most common site for urogenital tumors in children followed by ovaries (21%) and testis (13%). The uncommon sites included bladder (4%), prostate (2%), paratesticular tissue (1%), and vagina (1%) (Table 2).

Wilms tumor was the overall most common type of urogenital tumor which was seen in 55 (55%) patients and it also constituted most common type of renal tumors (94.82%). The triphasic tumors were composed of roughly



**Figure 1:** Gender distribution of the studied cases

equal proportions of all three elements in 90.91% (50/55). Blastema predominant tumors accounted for 1.82% (1/55), mesenchymal predominant tumors accounted for 1.82% (1/55), and epithelial predominant tumors accounted for 1.82% (1/55). Biphasic tumors were 3.64% (2/55); epithelial and mesenchymal and mesenchymal and blastemal components. There were no areas of cystic partially differentiated nephroblastoma or nephrogenic rests seen in these 55 cases (Figure 2).

TNM and NWTS system were used for staging. When the TNM staging was used, six tumors (10.91%) were staged as pT1, 3 (5.45%) were staged as pT2, and 1 (1.82%) of cases were staged as pT3c. Using the NWTS classification, 48 tumors (87%) were categorized as stage I, 1 (1.82%) each as Stages II and III, respectively, and 5 (9%) as stage V (Figure 2).

Mature cystic teratoma was overall the next most common tumor (13%) in our series, with 11/13 (84.62%) being found in the ovary. The remaining two (15.38%) were found in the testis. Mature cystic teratomas accounted for over half (52.38%, 11/21) of all our ovarian tumors. There were four girls and one boy with immature teratoma. The girls with immature teratomas of the ovary ranged from 6–14 years of age, with a mean age of 8 years. This final diagnosis was given as malignant tumor with immature epithelial and mesenchymal differentiation with a possibility of an immature teratoma (Figure 3).

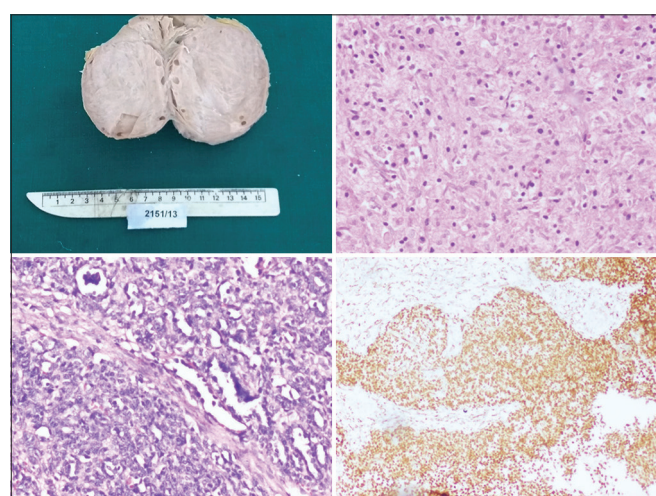
Mixed germ cell tumors accounted for 7% of the tumors in this series. Mixed germ cell tumors comprised 38.46% (5/13) of our testicular tumors and 9.52% (2/21) of our ovarian tumors. Testicular mixed germ cell tumors were seen in boys 1–14 years of age with a mean age of 9 years. Both girls with mixed germ cell tumors of the ovary were 14 years of age. Four of the five boys with mixed germ

Type of tumors (histopathology)	Frequency (N )	Location
Wilms tumor	55	Kidney
Mature cystic teratoma	13	Ovary – 11, Testis – 2
Mixed germ cell tumor	7	Ovary – 2, Testis – 5
Yolk sac tumor	6	Testis – 5, Vagina – 1
Rhabdomyosarcoma	6	Urinary bladder – 4 Paratesticular tissue and Prostate – 1
Immature teratoma	5	Ovary – 4, Prostate – 1
Juvenile granulosa cell tumor	2	Ovary
Sertoli-Leydig cell tumor	1	Ovary
Leydig cell tumor	1	Testis
Clear cell renal cell carcinoma	1	Kidney
Congenital mesoblastic nephroma	1	Kidney
Rhabdoid tumor of kidney	1	Kidney
Neuroblastoma	1	Paravesical tissue
Total	100	

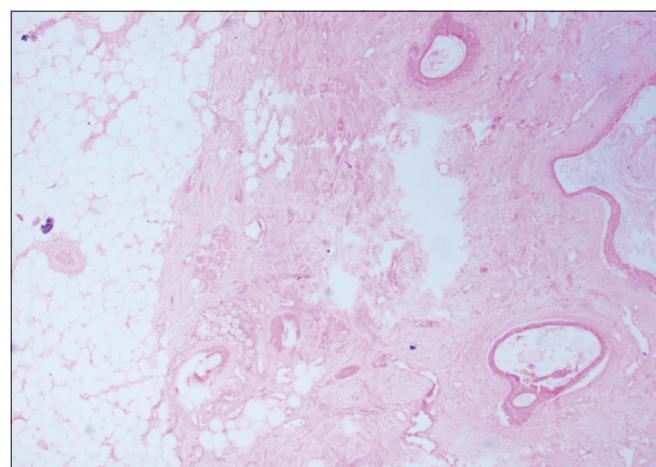
Site	Number of cases	Tumor	Frequency
Kidney	58	Wilms tumor	55
		Congenital mesoblastic nephroma	1
		Clear cell renal carcinoma	1
		Rhabdoid tumor	1
Ovary	21	Mature cystic teratoma	11
		Immature teratoma	4
		Mixed germ cell tumor	2
		Juvenile granulosa cell tumor	2
		Sertoli- Leydig cell tumor	1
		Dysgerminoma	1
Testis	13	Mixed germ cell tumor	5
		Yolk sac tumor	5
		Mature cystic teratoma	2
		Leydig cell tumor	1
Paratesticular	1	Rhabdomyosarcoma	1
Prostate	2	Immature teratoma	1
		Rhabdomyosarcoma	1
Bladder	4	Rhabdomyosarcoma	4
Paravesicle	1	Neuroblastoma	1
Vagina	1	Yolk sac tumor	1
Total	100		100

cell tumors of the testis (80%) presented with scrotal enlargement. Alpha fetoprotein levels in the serum were increased in three boys. Two showed elevated levels of beta HCG (40%).

Yolk sac tumors were seen in six children and accounted for 6% of our childhood tumors. Five were in the testis and comprised 38% of testicular tumors. The 6<sup>th</sup> tumor which was reported to be found in the vagina was excised elsewhere; the diagnosis was made on paraffin embedded



**Figure 2:** Wilms tumor (clockwise from left upper corner) gross appearance, immature mesenchymal, blastemal components, and immunohistochemistry



**Figure 3:** Mature cystic teratoma on H and E x100 magnification

tissue sent for review. Two of the testicular tumors were found in the right testis and two on the left side. All four tumors were well encapsulated, measuring 3.5–5 cm in maximum dimension with homogeneous gray tan cut

surfaces. One tumor showed foci of calcification, mucinous areas, and cystic change. Staging could be done in three patients. Two cases were staged as pT2 and one as pT1 (Figure 4).

There were six rhabdomyosarcoma (RMS) which accounted for 6% of our childhood tumors. Four were seen in the bladder, and one each in the prostate and paratesticular tissue. The diagnosis was based on core needle biopsy in three of the bladder tumors. Only one patient had a surgical resection (cystoprostatectomy) following chemotherapy. All tumors showed cells with eccentrically placed nuclei resembling rhabdomyoblasts and strap cells with striations in the cytoplasm, dispersed in an edematous and myxoid stroma. One bladder RMS (25%) showed tumor giant cells. One tumor (the resected specimen) had adjacent lymph nodes which showed reactive changes only.

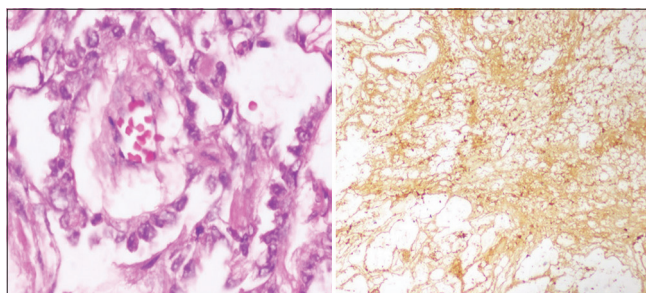
Immunohistochemistry could be done in two bladder tumors and the paratesticular RMS. All three showed positivity for myogenin and desmin. Immunohistochemistry was negative for CD99 and EMA. Only one of the six rhabdomyosarcomas could be staged. This was a bladder tumor which was staged as ypT2aN0Mx (Figure 5).

Juvenile granulosa cell tumor constituted 2% of the tumors in this series and 9.52% (2/21) of ovarian tumors. Both these tumors weighed 45 grams each and measured 4.6 cm and 6.5 cm in maximum dimension. The smaller one had a variegated cut surface with cystic areas and the larger had a lobulated cut surface.

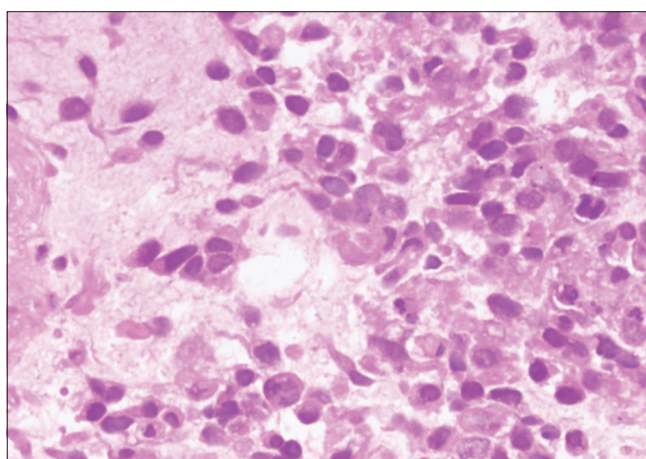
These tumors were arranged in nests, lobules, reticular, and macrofollicular pattern composed of polygonal cells with vesicular chromatin, prominent nucleoli, and eosinophilic cytoplasm. One case (the larger) had occasional cells displaying grooving. One (smaller tumor) case showed mitotic activity of 14/10 hpf in areas with cystic change, myxoid areas, and hemorrhage. Immunohistochemical stains were positive for alpha inhibin in both the cases and positive for calretinin (smaller tumor) and negative for PLAP (larger tumor) and cytokeratin (smaller tumor). Both these tumors were staged as pT1a (Figure 6).

Congenital mesoblastic nephroma comprised 1% of the tumors in our series and 1.72% (1/58) of the renal tumors. A 20-day-old baby girl was detected to have a right-sided renal mass on antenatal ultrasonography, at 7 months of intrauterine life. Prenatal ultrasound showed a soft-tissue mass in the lower pole of the right kidney.

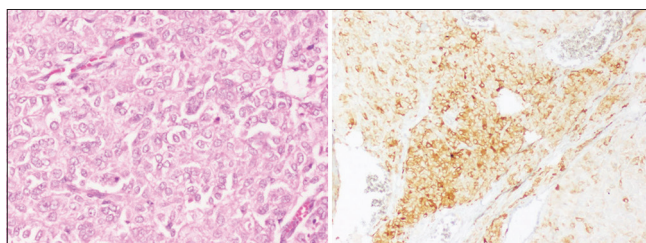
The tumor showed interlacing fascicles and bundles of spindle shaped cells with pleomorphic hyperchromatic nuclei and moderate eosinophilic cytoplasm. Mitotic



**Figure 4:** Schiller duval bodies in yolk sac tumor on H and E stain (left), alpha fetoprotein positivity on immunohistochemistry



**Figure 5:** Rhabdomyosarcoma on H and E stain x400 magnification



**Figure 6:** Juvenile granulosa cell tumor on H and E stain x200 magnification (left), alpha inhibin immunohistochemistry positivity (right)

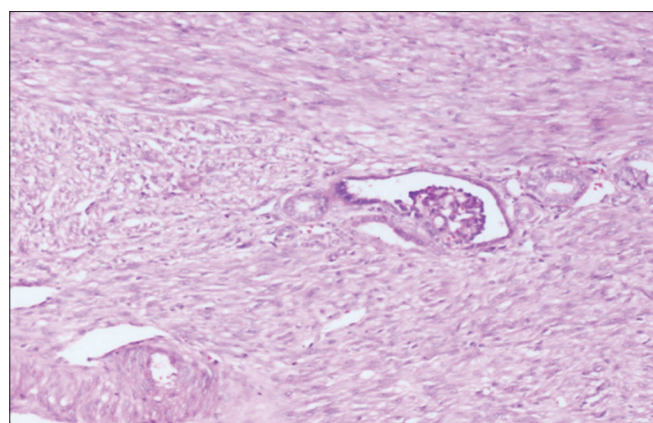
activity of 3–4/10 hpf was seen. Hyaline cartilage was seen within the tumor in one focus. Focus of entrapped glomeruli was seen (Figure 7). There was infiltration by into the renal sinus pad of fat. No immunohistochemical markers or special stains were done (Figure 7).

Clear cell carcinoma, Rhabdoid tumor of kidney, Sertoli-Leydig cell tumor, Leydig cell tumors, and neuroblastoma were less common form of urogenital tumors in our study. Summary of all urogenital tumors is given in Table 3.

## DISCUSSION

Wilms tumors accounted for the majority (91%) of our 58 children with renal tumors, similar to the literature. In keeping

Table 3: Summary of pediatric urogenital tumors in studied cases						
Tumor	Site	Median Age	No of cases	Distinctive features	IHC	Stage
Wilm's tumor (WT)	Kidney	3 years	55	9.4% – bilaterality Rhabdoid areas – 1	WT-1	NWTS Stage I- 46 cases
Congenital mesoblastic nephroma (CMN).		20 days	1	-	-	-
Clear cell RCC		14 years	1	H/o recurrence	-	-
Rhabdoid tumor		7 months	1	-	Vimentin, CD99 and myogenin.	-
Rhabdomyosarcoma (RMS)	Bladder	3.5 years	4	Tumor giant cells (1 case).	Desmin, myogenin	ypT2a (1 case)
Neuroblastoma		1 year	1	-	NSE, CD56, CD99, Synaptophysin and Vimentin	-
Immature teratoma	Prostate	4 years	1	Bladder infiltration	CD99, Synaptophysin, CK and FLI-1.	-
Rhabdomyosarcoma (RMS)		10 years	1	Lung and liver metastasis	-	-
Yolk sac tumor (YST)	Testes	1.8 years	4	Raised alpha fetoprotein.	AFP, PLAP (2 cases), OCT3/4 (1 case)	pT2 (2 cases) pT1 (1 case)
Mixed germ cell tumor		9.2 years	5	Raised alpha fetoprotein and beta HCG.	AFP, CD30 and PLAP (2 cases each) Beta HCG, CD117 and glypican-3 (1 case each).	pT3 (2 cases) pT2 (3 cases)
Mature cystic teratoma		2.5 years	2	-	-	-
Rhabdomyosarcoma (RMS)		12 years	1	-	Desmin and myogenin	-
Leydig cell tumor		5 years	1	Secondary sexual characters	-	pT1
Mature cystic teratoma	Ovary	10 years	11	Necrosis (15.4%)	-	-
Immature teratoma		8.2 years	4	Increased alpha fetoprotein (1 case)	-	-
Mixed germ cell tumor		14 years	2	-	-	pT1a (1 case) pT3cN1 (1 case)
Juvenile granulosa cell tumor		4 years	2	Secondary sexual characters	Alpha inhibin and calretinin	pT1a
Sertoli-Leydig cell tumor		5 years	1	Raised alpha fetoprotein and beta HCG	Alpha inhibin	-
Dysgerminoma		6 years	1	-	PLAP	-
Yolk sac tumor	Vagina	1 year	1	Increased LDH and AFP	Glypican-3	-



**Figure 7:** Entrapped glomeruli in congenital mesoblastic nephroma on H and E stain x100 magnification

with current practice, most tumors (58%) were diagnosed based on needle biopsies. In cases of Wilms tumor, the mean

age at presentation was 3 years with the majority of children presenting between 1 and 5 years of age. These findings were similar to other reports.<sup>11</sup> The male: female ratio of our patients was 1.5:1. This differs from the reports by Le et al., who showed a female preponderance and a higher incidence of these tumors in the Western population when compared to the Asians.<sup>12</sup> The gross features could be assessed in the 42% resected cases. The dimensions (22 cm), weight (238 g), and external and cut surfaces (solid cut surface in 54%, necrosis in 59%, and involvement of the entire kidney in 27%) were similar to other reports. A blastema-predominant pattern was seen in 2% of tumors and an epithelial predominant pattern in 2%. In contrast, 18% of the resected tumors reported by Webber et al., showed epithelial predominance and 39% showed blastema predominance.<sup>13</sup>

Mature cystic teratomas accounted for 85% of ovarian tumors and 15% of the testicular tumors in our study. The

majority of our ovarian teratomas presented between 10 and 15 years of age, with a mean age of 10 years, which is similar to other reports. The mean age of our children with mature cystic teratoma of the testis was 3 years, in contrast to other studies which have reported a mean age of 10–15 years in these patients.<sup>14</sup> The classical gross and microscopic features were seen in our patients, similar to what has been described earlier.<sup>15</sup>

Immature teratomas comprised 19% of all ovarian tumors in our study with a mean age of 8.2 years with classical gross and microscopic features as described in the literature. We had one immature teratoma of the prostate which presented as a cauliflower-like growth with sheets of pleomorphic tumor cells positive for CD99, synaptophysin, and FLI-1. Similar features are also described in literature by authors such as Depreest *et al.*<sup>16</sup>

In our study, mixed germ cell tumor accounted for 7% of tumors overall and 38% of testicular tumors and 10% of ovarian tumors. The most commonly seen component in both testis and ovary was yolk sac tumor (80% and 50%, respectively). Our findings are similar to a study by Sesterhen *et al.*, with respect to the components of these tumors. However, in contrast to our findings, Sesterhen *et al.*, found a yolk sac tumor component in 41% of their tumors with embryonal carcinoma in 47% and seminoma in 59%.<sup>17</sup>

Yolk sac tumors were seen in 6% of our patients. The mean age of children with yolk sac tumors was 1.8 years. Half the patients showed elevated serum alpha fetoprotein. The tumors were distributed equally between the right and left testis. The typical histological findings were seen, and there was positivity for AFP, PLAP, and OCT3/4. These findings were similar to the report of Wei *et al.*, except that their tumors were slightly more common in the right testis.<sup>18</sup>

Rhabdomyosarcoma accounted for 6% of tumors. The mean age of our patients was 3.5 years with a male: female ratio of 3:1. The microscopic appearance of these tumors was typical, with tumor giant cells in one case. Three out of six tumors showed positivity for myogenin and desmin. These features correlate with the published data.<sup>19</sup>

Juvenile Granulosa cell tumors accounted for 2% of all the tumors and 9.5% of the ovarian tumors. The gross and microscopic features and positivity for alpha inhibin and calretinin immunohistochemistry are similar to the literature. However, the mean age of our patients was 4 years, in contrast to the finding of Young *et al.*, who reported a mean age of 13 years.<sup>20</sup>

Gross and histopathological features of uncommon urogenital tumors such as congenital mesoblastic nephroma,

clear cell renal carcinoma, rhabdoid tumor of kidney, dysgerminoma, Sertoli-Leydig cell tumor, and neuroblastoma were found to be similar to various published studies on this subject.

#### Limitation of the study

The limitation of the study was that, in some cases, staging of tumors could not be done because in these cases trucut biopsy was done.

## CONCLUSION

Although uncommon urogenital tumors in pediatric age groups form one of the important causes, for which a pediatric urology consultation is sought. The most common urogenital tumor in pediatric age group is Wilms tumor which, mostly, presents in between 1 and 5 years of age. Wilms tumor is followed by mature cystic teratoma, mixed germ cell tumor, yolk sac tumor, rhabdomyosarcoma, and immature teratoma. Familiarity with the gross as well as microscopic features along with immunohistochemistry findings is essential in histopathological confirmation of diagnosis.

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**KV-** Concept and design of the study; interpreted the results, prepared first draft of manuscript and critical revision of the manuscript; **VMS-** Design of the study, Statistically analyzed and interpreted; reviewed the literature and manuscript preparation, revision of the manuscript, concept and coordination of the overall study; **RM-** Design of the study and revision of the manuscript.

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