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Case Series

Pathology Section

A Quaint Collation of Childhood Renal Neoplasms- Wilms and Beyond: Perspective of a Tertiary Care Hospital of Eastern India

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ABSTRACT

Paediatric renal neoplasms are rarely encountered entities. Histopathology is essential in most of the cases, where there is significant degree of clinical and radiological overlap. Present series has 32 cases which aimed to evaluate clinical and pathologic spectrum of renal tumours in children. Nephrectomy specimens of renal neoplasms of children below 12 years of age were included. Haematoxylin and Eosin (H&E) staining and Immunohistochemistry (IHC) were done. Findings were tabulated in a master sheet along with other demographic variables, clinical histories and imaging findings. Abdominal lump was the commonest presentation. Wilms tumour was the major histologic variant (66%), followed by Congenital Mesoblastic Nephroma (13%). Anaplasia and advanced Children's Oncology Group (COG) staging were the adverse prognostic indicators. Clear Cell Sarcoma and Rhabdoid tumours were seen to have adverse outcomes, whereas Congenital Mesoblastic Nephroma, Multicystic Dysplastic Kidney and Paediatric Cystic Nephromas had overall favorable prognosis. Histopathology plays a key role for confirmatory opinion on nature of the neoplasm. Better understanding of these cases will increase the diagnostic accuracy with early implementation of definitive therapy.

Keywords: Clear cell sarcoma, Congenital mesoblastic nephroma, Cystic nephroma, Multicystic dysplasia, Rhabdoid tumours

INTRODUCTION

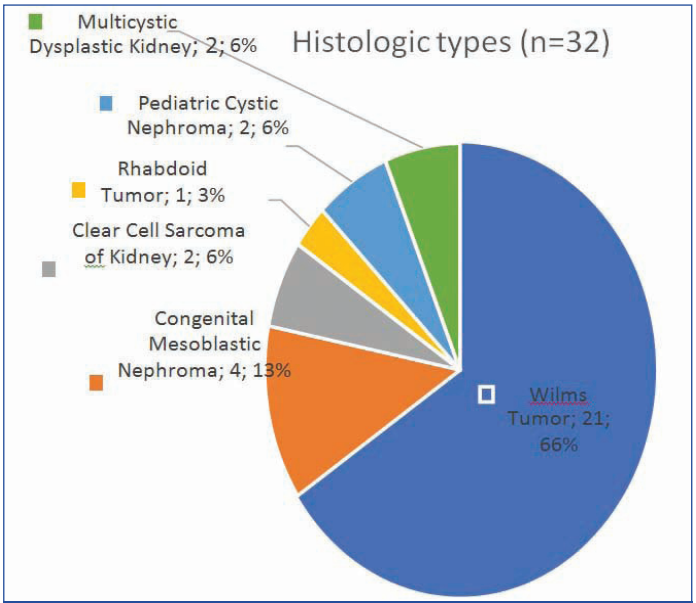
Paediatric renal neoplasms are rare and often detected incidentally during routine clinical examination [1]. They lack specific symptomatology and hence, pose a diagnostic challenge not only to the clinician but also to the reporting pathologists. Seven percent (7%) of all malignant childhood tumours are of renal origin. This entity is a heterogenous group with wide histopathologic spectrum from non-neoplastic, to benign and malignant lesions, each with widely different therapeutic approach [2]. A vast majority of 90% of pediatric renal tumours belong to the category of Wilms Tumour, the other rare variants being Clear Cell Sarcoma of the Kidney (CCSK), Malignant Rhabdoid Tumour of the Kidney (MRTK), Congenital Mesoblastic Nephroma (CMN) and others [3]. Histopathology is the key to diagnose these neoplasms with very distinct morphologic patterns. However, some of these neoplasms have a considerable degree of histopathological overlap, where ancillary studies like IHC plays an important role to unveil the exact nature of the tumour.

The present article is a case series of 32 cases done in a tertiary care centre in Eastern India, where all cases of paediatric renal neoplasms were studied along with suitable ancillary investigations, where applicable, to arrive at definitive diagnosis and guide the mode of treatment. The study was conducted for a total duration of seven years from March 2014-March 2021. Children below 12 years of age underwent Nephrectomy after obtaining informed consent from the patient relatives. The specimen were grossed, followed by H&E staining. Ancillary studies like IHCs were done for suitable cases and detailed history along with imaging reports were considered before delivering the final diagnosis.

CASE SERIES

The distribution of cases as per their histologic types is shown in [Table/Fig-1].

Wilms Tumour (WT): A total of 21 (66%) cases were Wilms tumour, with equal sex distribution (male- 11 cases; 52% and female- 10 cases; 48%); mean age of presentation being 24 months (range- 13-44 months). Common presenting features were abdominal lump and pain; haematuria in four cases (19%) and hypertension in five cases (24%) were seen [Table/Fig-2].



[Table/Fig-1]: Distribution of paediatric renal neoplasms as per their histologic types (n=32).

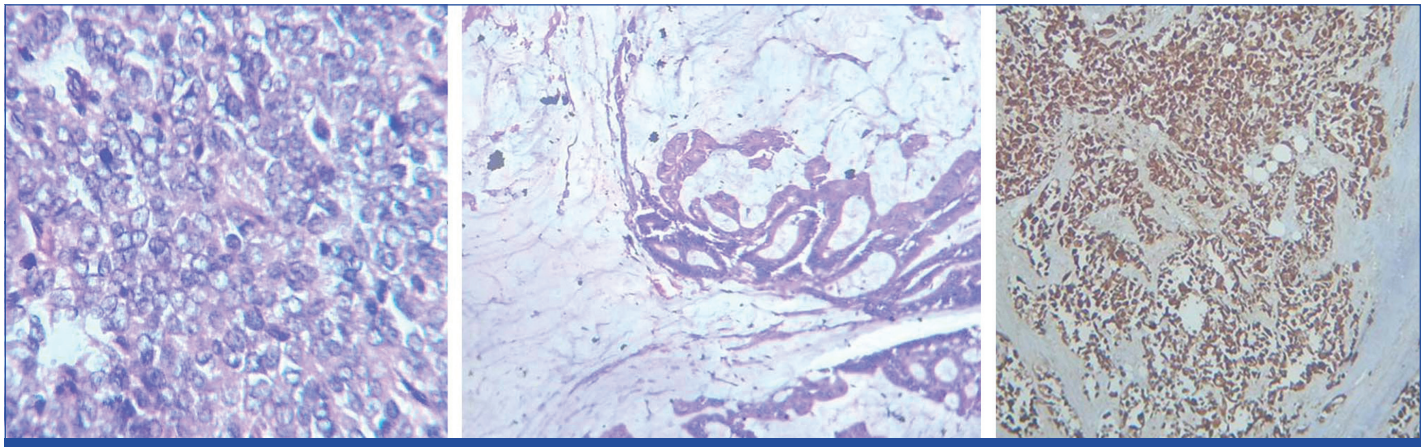
The institute followed the treatment guidelines as per National Wilms Tumour Study Group (NWTSG)/Children's Oncology Group (COG), where primary resection followed by chemotherapy was the main modality of treatment [4]. All specimens received were that of Radical Nephrectomy; common gross findings being unilateral and unifocal tumour masses with solid, multinodular, tan grey appearance. The range of tumour dimension was 6.5-17 cm. All 20 cases were triphasic Wilms tumour, amongst which, two rare variants were seen- one being diffuse blastemal pattern [Table/Fig-3], which grossly was the largest tumour and second being Teratoid Wilms tumour [Table/Fig-4], which was multifocal with areas of cystic degeneration. A single case of monophasic Wilms Tumour with only blastemal component was seen and confirmed by diffuse Wilms Tumour (WT1) nuclear positivity [Table/Fig-5]. As per COG staging, 15 cases (71%) were Stage I, 4 (19%) were Stage II and rest 2 (10%) comprising monophasic Wilms tumour

Parameters		Number (n)	Percentage (%)
Gender	Male	11	52
	Female	10	48
Clinical presentation	Abdominal pain, swelling	21	100
	Haematuria	4	19
	Hypertension	5	24
Histopathological pattern	Triphasic Wilms	20	95
	Monophasic Wilms	1	5
Children's Oncology Group (COG) stage	Stage I	15	71
	Stage II	4	19
	Stage IV	2	10
Anaplastic features	Focal	2	9
	Diffuse	1	5
	Absent	18	86
Follow-up	Death	4	19
	Good response	17	81

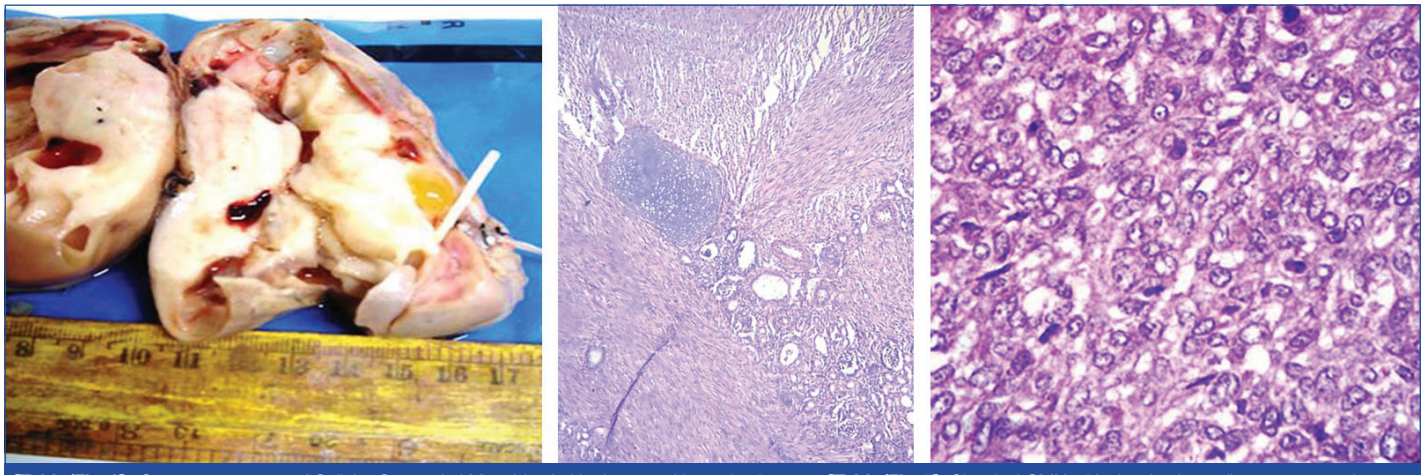
[Table/Fig-2]: Distribution of Wilms tumour cases as per their demography, clinical features, histopathological pattern, staging, anaplastic features and postsurgical follow-up (n=21).

of them presented with abdominal masses. There were no feeding complaints or other urinary symptoms. On detailed evaluation, one mother gave history of polyhydramnios, other obstetric histories being uneventful. Ultrasonography showed well-defined mass in the unilateral kidneys. There were concentric echogenic and hypoechoic rings in three cases; whereas one case showed cystic changes within the tumour. Nephrectomy in all the cases showed well-defined masses on medial side of the kidneys with whitish, whorled appearance. They were predominantly firm, whereas friable with areas of cystic degeneration [Table/Fig-6] and haemorrhage in one case, which corroborated with the imaging findings of these cases. The gross mean dimension of the tumour was 5 cm. On histopathologic examination, three cases were that of classical CMN and one case with friable consistency was cellular CMN. The classic variant showed dysplastic cartilage in the adjacent renal parenchyma [Table/Fig-7]; whereas the cellular variant had brisk mitosis [Table/Fig-8]. All the resection margins, including the medial margin were free from tumour and were Stage I.

Follow-up of all the three cases of classic CMN showed good prognosis, with no recurrence within three years of follow-up, till the preparation of this manuscript. The cellular CMN presented with



[Table/Fig-3]: Diffuse blastemal pattern (H&E, 400x magnification); **[Table/Fig-4]:** Extensive mucinous differentiation in teratoid Wilms tumour (H&E, 100x magnification); **[Table/Fig-5]:** WT1 (nuclear) positivity in monophasic Wilms tumour (100x magnification). (Images from left to right)



[Table/Fig-6]: Gross appearance of Cellular Congenital Mesoblastic Nephroma with cystic changes; **[Table/Fig-7]:** Classical CMN with dysplastic cartilage, entrapped tubules and glomeruli (H&E, 100x magnification); **[Table/Fig-8]:** Cellular CMN with brisk mitosis (H&E, 400x magnification). (Images from left to right)

and diffuse blastemal pattern were Stage IV. Amongst Stage II, two cases showed focal anaplasia, whereas, one Stage IV case of monophasic Wilms tumour had diffuse anaplasia. On follow-up, both Stage II cases displaying focal anaplastic features and two Stage IV cases died within two years of follow-up. Rest of the cases (17 cases) had been put on chemotherapy and were doing well for five years post-surgery till the presentation of this study.

Congenital Mesoblastic Nephroma (CMN): A total of four cases (13%) were that of CMN, comprising two males and two females. Three cases were one month old and one case aged six months. All metastasis to retroperitoneal lymph nodes within two years of surgery and was put under chemotherapeutic regimen [Table/Fig-9].

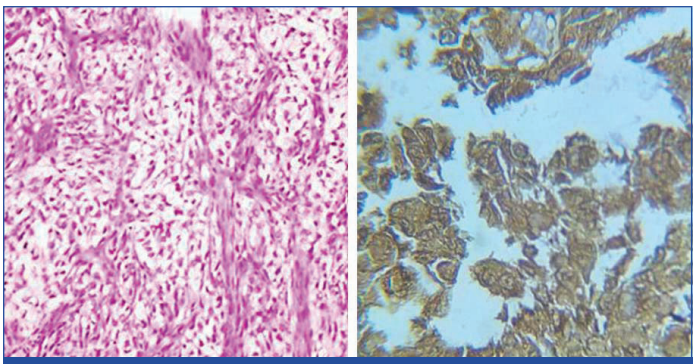
Clear Cell Sarcoma of Kidney (CCSK): A total of two cases (6%) were of Clear Cell Sarcoma of unilateral Kidney, both seen in male child. Their ages were 12 months and 24 months respectively. They presented with abdominal masses. Computed Tomography (CT) images showed large heterogeneously enhancing masses measuring 11.5 and 14 cm respectively, centered around renal medulla. They underwent nephrectomy with suspicion for Wilms tumour in a peripheral centre followed by H&E and IHC examinations. The cases

Parameters		Number	Percentage (%)
Gender	Male	2	50
	Female	2	50
Clinical presentation	Abdominal Mass	4	100
Gross appearance	Solid, firm, whitish	3	75
	Solid-cystic, whitish, friable	1	25
Histopathological variant	Classic	3	75
	Cellular	1	25
Follow-up	Good	3	75
	Metastasis to retroperitoneal lymph nodes	1	25

[Table/Fig-9]: Distribution of Congenital Mesoblastic Nephroma as per their demography, clinical presentation, gross appearance, histopathological variant and follow-up (n=4).

were reviewed and re-evaluated in our department with all ancillary studies for confirmatory opinion before initiation of chemotherapy.

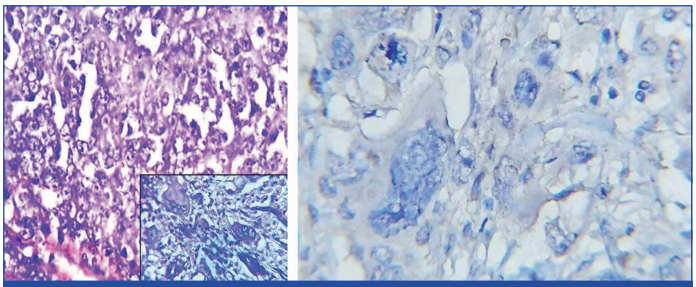
Grossly, the mass was unifocal, well-circumscribed but unencapsulated, pale-creamy with mucoid, cystic and focal necrotic areas as per the documentation in the histopathology report. Sections showed uniform cells separated by delicate capillary network of vessels, clear to granular cytoplasm, finely dispersed chromatin and inconspicuous nucleoli. Myxoid stroma with entrapped tubules and glomeruli were noted at the infiltrating border of the tumour. There were no tubular or blastemal components in any of the sections. Thus, a diagnosis of classic CCSK was made [Table/Fig-10]. This was further substantiated by Cyclin D1 positivity in tumour cells [Table/Fig-11] as per the IHC slides that were reviewed. One case was Stage I and another was Stage II with infiltration of renal capsule and peri-sinus fat.



[Table/Fig-10]: Classic CCSK (H&E, 400x magnification).
[Table/Fig-11]: Diffuse Cyclin D1 positivity in CCSK (400x magnification). (Images from left to right)

Postsurgery, all cases were put to chemotherapeutic regimen. One case lost follow-up, whereas the other succumbed to death within two years due to brain metastasis.

Rhabdoid tumour: There was 1 (3%) case of Rhabdoid tumour in a male baby of 12 months, who presented with abdominal mass and haematuria. The CT scan showed a 16 cm tumour, involving almost the whole of unilateral kidney with metastasis to ulna. Radical nephrectomy was done. This was actually a review case, who had undergone the surgery along with histopathology and IHC from a peripheral centre and was referred to this institute for re-evaluation, further follow-up and treatment. Grossly the tumour involved the resection margins; with pale creamy colour and wide areas of haemorrhage and necrosis as was detailed in the original histopathology report. The H&E showed large atypical rhabdoid cells with vesicular chromatin, prominent nucleoli and eosinophilic hyaline cytoplasmic inclusions [Table/Fig-12]. Additionally, there was loss of SMARCB1 expression [Table/Fig-13] as was seen in the received IHC slide. A diagnosis of Rhabdoid tumour of kidney (Stage IV) was confirmed for initiation of treatment.

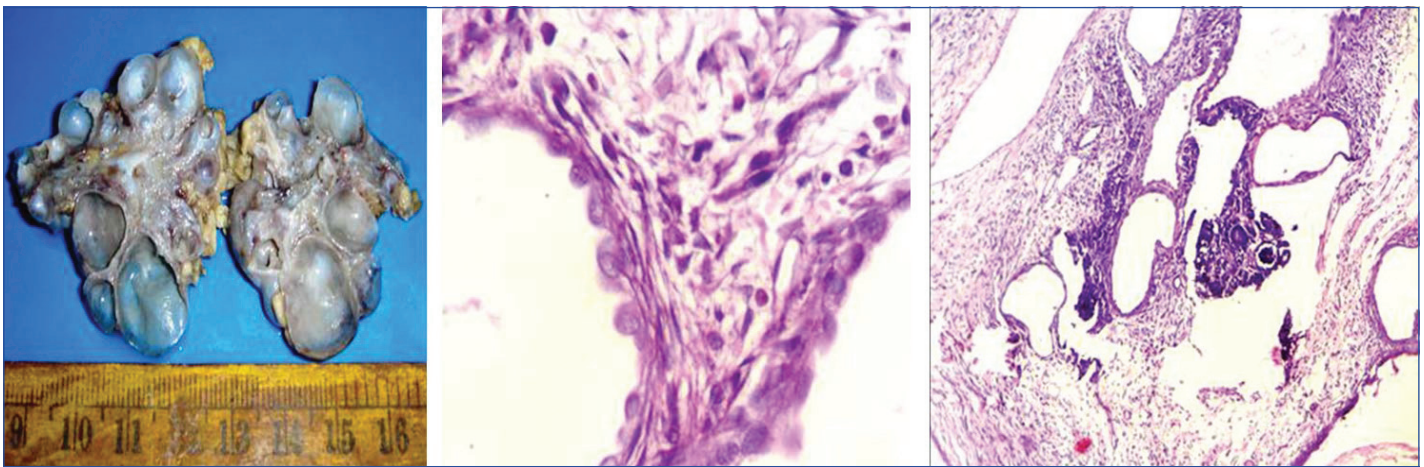


[Table/Fig-12]: Rhabdoid tumour of kidney, inset shows cells with prominent nucleoli and tumour giant cells (H&E, 400x magnification).
[Table/Fig-13]: Loss of SMARCB1 in Rhabdoid tumour of kidney (400x magnification). (Images from left to right)

Post-surgery, he was put on chemotherapeutic regimen. However, the patient died within one year of follow-up.

Paediatric cystic nephroma: There were two cases (6%), comprising one male and one female aged 12 and 16 months respectively. They presented with abdominal masses. Ultrasound showed large cystic spaces involving almost the whole of unilateral kidney. Nephrectomy was done. Gross inspection showed well-circumscribed, cystically dilated kidney measuring 9.5 and 12 cm respectively with loss of cortico-medullary differentiation [Table/Fig-14]. The H&E sections showed multiple cystic spaces lined by hobnail [Table/Fig-15], cuboidal or denuded epithelium. The septas had fibrous tissue with focal cellular condensation and entrapped tubules [Table/Fig-16], without any solid neoplastic nodules or immature nephroblastic elements. Thus, the diagnosis of Pediatric Cystic Nephroma was offered. Both the patients were doing well on long term follow-up for upto three years till the publication of this manuscript.

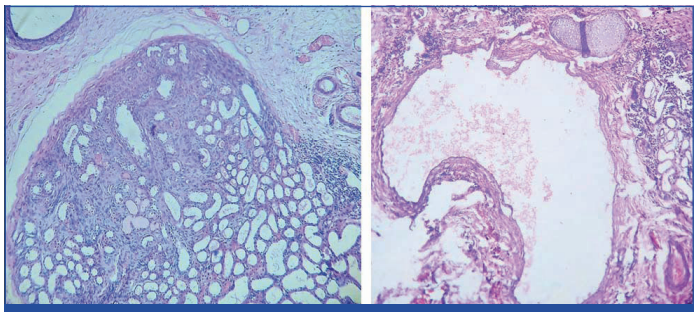
Multicystic Dysplastic Kidney (MCDK): Total two cases (6%) of MCDKs were seen. One case was diagnosed during pre-natal ultrasound; another presented as newborn flank mass. The



[Table/Fig-14]: Gross picture of paediatric Cystic nephroma; **[Table/Fig-15]:** Cyst lined by Hobnail epithelium in Pediatric Cystic Nephroma (H&E, 400x magnification); **[Table/Fig-16]:** Cyst with focal cellular condensation and entrapped tubules (H&E, 100x magnification). (Images from left to right)

malformation was unilateral with no associated anomalies of other organ systems. Ultrasonography showed large spherical cysts with non-delineation of the renal sinus.

Nephrectomy specimen showed cystically dilated spaces in unilateral kidney. Histopathological examination showed metaplastic cartilage, primitive ducts with lobar disorganisation [Table/Fig-17,18]. Thus, a diagnosis of MCDK was given. Long-term follow-up of the cases has shown good prognosis with normal functioning of contralateral kidney.



[Table/Fig-17]: Primitive ducts with lobar disorganisation in MCDK (H&E, 100x magnification). **[Table/Fig-18]:** Metaplastic cartilage with primitive ducts in MCDK (H&E, 100x magnification). (Images from left to right)

DISCUSSION

Paediatric renal neoplasms are challenging to the clinician as they present with abdominal mass with overlapping imaging findings. Histopathological study is often the mainstay for arriving at definitive diagnosis. They create diagnostic dilemmas to the surgical pathologists due to their undifferentiated nature and wide histologic diversity that often mimics various renal and extra-renal neoplasms with potential for significant diagnostic error. Lack of daily experience further complicates the task of the pathologists, who are not familiar with these entities in day-to-day practice [5].

The mean age of the study population of 32 cases was 20 months, youngest being the newborn with Multicystic Dysplastic Kidney (MCDK) and oldest being 44 months in a Wilms tumour case. This is significantly lower than that of Bozlu G and Çıtak EÇ, where the mean age of all cases was 53.26±46.64 months [6]. This may be due to the widely heterogenous non-Wilms tumour neoplasms that vary widely in their incidence with significant variation in their demographic characteristics. The male paediatric cases were 59% (19 cases out of 32). These statistics are dominated by the Wilms tumour group that formed the majority (66%) of the study population which was at par with the other studies [6-8]. Among non-Wilms tumour group, the most common histologic type was Congenial Mesoblastic Nephroma (13%), followed by Paediatric Cystic Nephroma, CCSK and MCDK (each being 6%). This was similar to the study conducted by Glick et al., [9].

Abdominal mass was the common presenting feature in all these cases, whereas few cases of Wilms tumour presented with haematuria and hypertension, as was also observed by Lamb MG et al., [10]. Rhabdoid tumour case had features of distant metastasis during its presentation, which itself was a bad prognostic indicator. Similar cases have also been documented in the literature, thereby indicating the very aggressive nature of the neoplasm and its tendency for early metastasis [11].

The typical triphasic pattern is very diagnostic of Wilms tumour where histomorphology is sufficient to arrive at the definitive diagnosis, except for special cases like Monophasic Wilms tumour. WT1 positivity was utilised in that case to differentiate it from non-Wilms neoplasms, as was also demonstrated by Goyal S et al., [12]. Of special mention, was a rare histologic variant namely Teratoid Wilms tumour which belongs to the extreme end of the spectrum of Triphasic Wilms tumour with very few reported cases in the literature and high mortality rate [13]. However, this case was doing well till five years post-surgery with good chemotherapeutic response. A very potent prognostic indicator of Wilms tumour, i.e., anaplasia was present focally in about 9% and diffusely in about 5% cases, which was at par with the observation of 5% by Davidoff AM [14]. Cases with focal to diffuse anaplasia and diffuse blastemal pattern were considered as adverse prognostic factors in Wilms tumour, all these cases dying within two years of follow-up, which was at par with the review article authored by Vujanić GM et al., [15].

A very significant history of polyhydramnios was evaluated in one of the cases of CMN, which was observed to be commonly reported by Daskas N et al., [16]. The gross morphologic appearances of cellular and classical CMN were similar to the findings by Chaudry G et al., [17]. Cellular CMN is a bad prognostic indicator [18] as was also seen in present case that presented with metastasis within two years of follow-up.

The CCSK per se is a rare and very aggressive neoplasm of kidney with very poor prognosis [19]. This was reflected by death of one out of two cases even after chemotherapeutic treatment. The confirmation of histomorphologic diagnosis was Cyclin D1 positivity by IHC that has recently been found to be a very useful marker to differentiate it from blastema-rich Wilms tumour [20], which was that main differential of present case.

Rhabdoid tumours of kidney have a dismal prognosis which is further potentiated by presence of metastasis at the time of presentation as was demonstrated by Reinhard H et al., [21]. This was observed in this study as well, where the case being Stage IV died within one year of follow-up. Its diagnosis was strengthened by loss of immunohistochemical expression of SMARCB1 that differentiated it from Renal Cell Carcinoma with rhabdoid features, as has been demonstrated in a similar study by Han E et al., [22].

Paediatric cystic nephromas usually have a benign course with good prognosis following nephrectomy [23], as was seen in this study population. Histomorphology is very important to differentiate it from Cystic Partially Differentiated Nephroblastoma (CPDN) which is characterised by presence of immature nephrogenic elements [24].

Prognosis of MCDK is dependent on timely diagnosis with associated foetal anomalies [25]. In this study, since both the cases were devoid of any other malformations, they carried a very good overall prognosis.

Thus, it is clear that a combination of careful gross examination followed by detailed histomorphological and immunohistochemical evaluation is required to arrive at a correct diagnosis. It is important as these tumours range from those which do not require chemotherapy and follow-up (e.g., Mesoblastic nephroma (Classic), Pediatric Cystic Nephroma) to those with a prognosis far worse than the usual favorable histology Wilms tumour (e.g., clear cell sarcoma, rhabdoid tumour) and varying chemotherapeutic regimen. Thus, a better understanding of these cases shall increase the diagnostic accuracy of these neoplasms with improved scope of treatment and favorable outcome for the patients.

CONCLUSION(S)

Wilms tumour was the most common renal neoplasm in paediatric age group followed by CMN. Although the former mostly had a favourable outcome, anaplasia and advanced COG staging were the adverse prognostic variables in this group. CCSK and Rhabdoid tumours were the most aggressive amongst non-Wilms tumour category. Pediatric Cystic Nephromas and MCDKs were seen to have favourable outcomes.

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All the co-authors have contributed equally to the preparation of the manuscript. This is an original work that has not been produced in any form in any other platforms.

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