Original Article

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Clinicopathologic Analysis of Wilms' Tumor: A Retrospective Study of 35 Cases Over 10 Years

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ABSTRACT

Background: Wilms' tumor is the commonest pediatric renal tumor and has a peak incidence between two and five years of age. Clinicopathological staging of Wilms' tumor is the single most important prognostic determinant and therefore histopathological analysis is important.

Methods: This is a retrospective study of diagnosed cases of Wilms' tumor received as surgical and autopsy specimens in the department of pathology in a major teaching hospital over a period of ten years. Clinical, biochemical and radiological details were retrieved from medical records. Information regarding routine gross and microscopic examination findings (paraffin sections) was retrieved from departmental records

Result: We received 24 nephrectomies, three post mortem specimens and eight biopsies. Maximum cases were found between two to five years of age with no gender predilection. Most patients presented with abdominal lump. Grossly, majority specimens had a variegated cut surface whereas two cases had a predominantly cystic appearance. Microscopically, 26 cases showed classic triphasic histology. Eight out of 27 cases (nephrectomies and post mortem cases) received preoperative chemotherapy. All cases showed extensive chemotherapeutic response and one case showed post – chemotherapy change mimicking a cystic partially differentiated nephroblastoma (CPDN). Of the remaining 19 cases which did not receive chemotherapy, only one case had an unfavorable histology. A rare case of CPDN was reported.

Conclusion: Histopathologist plays an important role in the diagnosis of Wilms tumor. Clinical, radiological and pathological correlation is necessary in the final reporting of these cases.

Keywords: *Wilms' Tumor, Pediatrics, Triphasic*

Introduction

Wilms' tumor is the commonest pediatric renal tumor and comprises 85% of these tumors. It has a peak incidence between two and five years of age and the patients usually present with an abdominal mass. [1] The commonest histologic subtype of Wilms' tumor is the classic triphasic type. The presence of anaplasia differentiates favourable from unfavourable histology. Histopathology, percentage response to chemotherapy and clinicopathological staging of Wilms' tumor are the most important prognostic determinants and play a decisive role in further management of the patient. This highlights the importance of a complete histopathology report in such cases. It is very important to differentiate Wilms' tumor from other pediatric renal tumors owing to availability of excellent chemotherapeutic regimen. Even in a large medical center, Wilms' tumor constitutes only a small percentage of surgical pathology workload. There are very few Indian publications dealing with pathology of Wilms' tumor. Hence, we felt that a pathologic analysis of Wilms' tumor with clinicoradiologic correlation would be a useful exercise.

Materials and Methods

This is a retrospective study of 35 diagnosed cases of Wilms' tumor received as surgical and autopsy specimens in the department of Pathology over a period of ten years. All specimens received were grossed and processed as per the standard method. Clinical information and details of biochemical, radiological and other investigations were obtained from the indoor charts. Information regarding gross and microscopic features was retrieved from departmental records. The pathologic parameters assessed were:

Gross features: The size and weight of the specimen, the status of the renal capsule, the involvement of renal sinus, presence of necrosis and the status of the margins of resection.

Microscopic Features: Overall pattern of the tumor (nodular or diffuse), number of components (blastemal, mesenchymal or epithelial) with a mention of the predominant component**,** presence of heterologous elements if any**,** presence of anaplasia**,** mitotic activity, presence of nephrogenic rests and chemotherapy induced

changes (including percentage of viable tumor and percentage of necrosis in post chemotherapy specimens).

Result

The cases comprised 24 nephrectomies, three post mortem specimens and eight biopsies.

Demographic Data: The age of patients ranged from 6 months to 9 years. Maximum cases (n= 22) were found between 2 and 5 yrs of age. Girls were affected more than boys. We did not find any case of Wilms' tumor in adults.

Clinical Data: All patients (n=35) presented with an abdominal lump. The other presenting complaints were: abdominal pain (10 cases, 28.5%), fever (7 cases, 20.58%) and hematuria (3 cases, 8.82%). In addition, four cases (11.76%) were hypertensive and anemia was detected in seven patients (20.58%). Two patients developed veno occlusive disease after receiving chemotherapy. One out of these two patients succumbed to death within six hours of receiving the chemotherapy and is an autopsy case. Associated diseases noted in our study included Ewings sarcoma (one case) and Thalassemia intermedia (one case-confirmed by hematologic tests).

Biochemical Investigations: Renal function tests were performed in ten patients. Serum levels of blood urea nitrogen (BUN) and serum creatinine ranged from 4.5 to 18.2 mg/dl and 0.4 to 0.9 mg/dl respectively.

Radiological Investigations: Thirty three out of 35 cases had Ultrasonography (USG) and/or Computed tomography (CT) scan performed. Scans were not performed in two patients due to death of patient within few hours of admission. Nineteen out of 20 cases in whom USG was performed, a diagnosis of Wilms' tumor was rendered. Only one case had a diagnosis of neuroblastoma instead of Wilms' tumor. Wilms' tumor was reliably diagnosed in 30 out of 32 cases in whom CT scan was available. Five cases showed inferior vena cava thrombosis and seven cases had findings suggestive of metastasis to the lung, lymph node or the liver. Metastasis to two or more than two sites was seen in four cases, of which one patient succumbed to death. Three cases showed prominent cystic areas within the tumor which correlated with the gross findings of the specimens received in our department.

Renal Doppler showed thrombosis in two cases and two dimensional echocardiography showed an atrial mass in one patient.

Chemotherapy: Eight cases received neoadjuvant chemotherapy of which seven were surgical resections and one was an autopsy case. Five out of seven cases had undergone a prior biopsy. The patients received four cycles of vincristine, dactinomycin and doxorubicin.

Gross Features: (Table 1) Gross features of 24 nephrectomies and 3 autopsies were noted, the remaining being biopsy specimens. The maximum and minimum size of tumor found in our study was 35x20x10cm and 4x2.5x2cm respectively. The weight of tumor ranged from 100 gram to a maximum of 3 kilogram. A single case of an extra renal Wilms' tumor was reported (suprarenal in position). Almost all tumors showed a variegated cut surface (Fig 1a) except two cases which were predominantly cystic, one of which was a cystic partially differentiated nephroblastoma (Fig 1b) and the other was a post – chemotherapy change (Fig 1c). All post – chemotherapy excision tumor specimens showed hemorrhage, necrosis, cystic change of variable degree & one case showed cartilaginous change (Fig 1d).

Histological features: (Table 2)

Resection specimens - All cases showed all three components namely epithelial, mesenchymal and blastemal and hence belonged to triphasic type of Wilms' tumor. The predominant component was blastemal component in cases which had not received chemotherapy (Fig 2a &b). Variable degree of necrosis and mitotic activity was seen in all tumors even without neoadjuvant chemotherapy. Focal anaplasia was recorded in one tumor thereby suggesting unfavorable histology.

In post chemotherapy specimens, no blastemal component was seen which suggests that it was the component which responded to chemotherapy and underwent necrosis. Cystic change, the most commonly noted change, was seen focally in majority of cases whereas one case showed extensive cystic change (Fig 2c &d). Another case showed predominance of epithelial component suggesting that it was either chemoresistant or a maturation effect. In post chemotherapy specimens, necrosis and hemorrhage was seen in all cases and inflammation in few cases but two patients showed post – chemotherapy maturation of epithelial and mesenchymal components (1 case each). It was seen in the form of keratinising squamous epithelium, cartilage, osteoid and rhabdomyomatous component. (Fig 3a,b,c & d)

The remaining 19 cases which did not receive any chemotherapy (2 autopsy cases and 17 surgical cases), comprised a rare case of CPDN, a case with unfavorable histology (focal anaplasia) and other cases with classic triphasic histology.

Biopsies: We received a total of 13 biopsies in our study, of which 5 were performed for administering neoadjuvant chemotherapy and were received along with post nephrectomy specimens, hence not counted separately. The remaining 8 cases were received as only biopsies. A

confident diagnosis of Wilms' tumor was given in nine cases whereas differential diagnosis (neuroblastoma in two cases, ganglioneuroblastoma and rhabdoid tumor in one case each) was given in four cases.

Metastasis: Two autopsy cases and one surgical case showed extension of tumor into the right atrium. One of the two autopsy cases also showed pulmonary and hepatic metastasis. (Fig 4a, b, c &d)

Table 1: Gross features of nephrectom specimens

Gross features	No. of cases (n=27)
Location – Renal Extra renal	26 01 (suprarenal)
Tumor size range	4x2.5x2 cm - 35x20x10cm
Weight range	100gm - 3kg
Cut surface –Variegated Predominantly cystic	25 02(1 case post chemotherapy)
Extension of tumor into right atrium	03 (2 autopsy cases and 1 surgical case)
Involvement of renal capsule	7
Involvement of renal sinus	9
Involvement of resection margins 1.Renal vein 2.Renal artery	8 5 3
Chemotherapy given	8 (7 surgical resections and 1 autopsy case)
Effects of chemotherapy 1.Necrosis and hemorrhage 2.Extensive cystic change	8 1

Table 2: Microscopic features of Nephrectomy specimens only.

Microscopic Feature	No. of cases
Components – Triphasic Biphasic Monophasic	27 - -
Necrosis	19
Mitotic activity (variable maximum 5 mitosis/hpf)	27
Anaplasia	1
Nephrogenic rests	0
Unusual (unfavourable) histologic subtype Classic CPDN	**1** 1
Heterologous elements – Epithelial Mesenchymal	**2** 1 1
Chemotherapy induced changes(n=8) Necrosis (40 % to 90%) Hemorrhage Fibrosis Foamy histiocytes Metaplasia Inflammation Extensive cystic change	 7 6 1 3 1 5 1

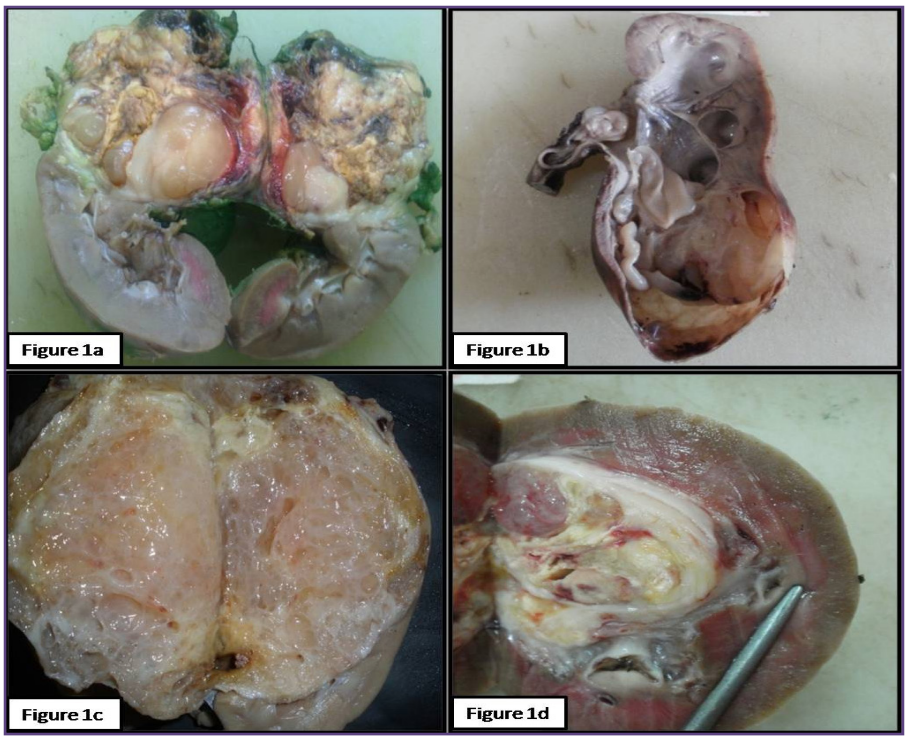

Fig. 1: 1a - Variegated appearance of Wilms' tumor on cut surface ; 1b - Cut surface of a Cystic Partially Differentiated Nephroblastoma (CPDN); 1c - Cut surface of post - chemotherapy cystic change in Wilms' tumor; 1d- Cut surface showing cartilaginous component in a post - chemotherapy specimen of Wilms' tumor.

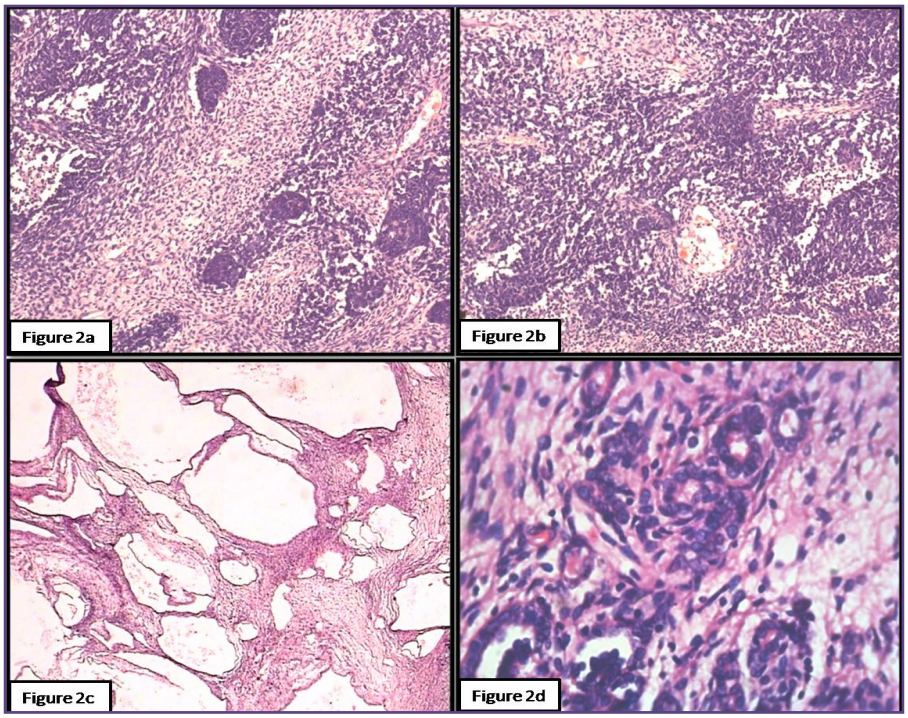

Fig. 2: 2a- Triphasic Wilms' tumor with predominant blastemal component (H&E, x100); 2b- Triphasic Wilms' tumor (H&E, x100); 2c- Extensive cystic change in a postchemotherapy specimen (H&E, x40); 2d- Presence of epithelial component in the form of tubules and glomeruloid forms in an extensively cystic post-chemotherapy specimen (H&E, x400).

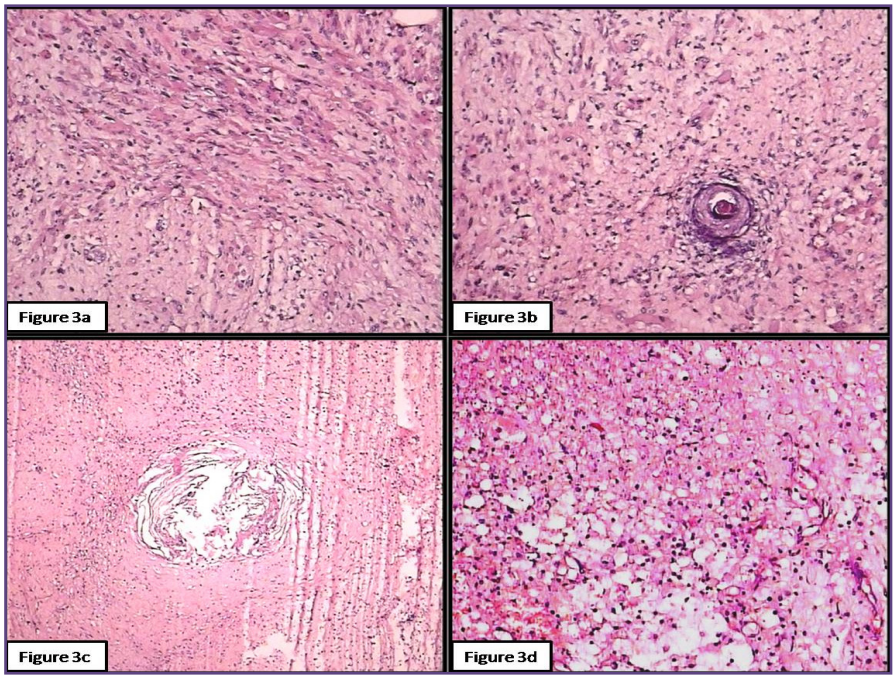

Fig. 3: Post chemotherapy changes: 3a- Rhabdomyoblastic differentiation (H&E, x100); 3b- Squamous differentiation (H&E, x100); 3c- Squamous differentiation and keratinisation (H&E, x100); 3d- Inflammation, foamy macrophages and hemorrhage (H&E, x100).

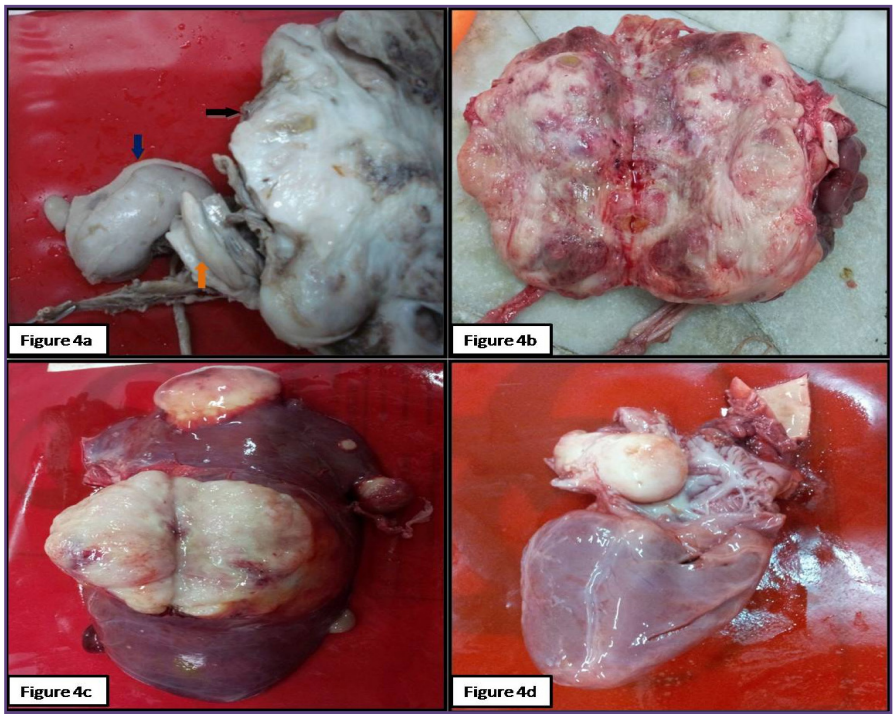

Fig. 4: 4a- Kidney urinary bladder (KUB) block of Wilms' tumor in an autopsy case. On left side is the opposite normal kidney (↑) and On right side is the tumor occupying the entire kidney (➜) and in between is the Aorta and Inferior Vena Cava. Tumor thrombus is seen in the in the Inferior vena cava (↓) 4b- Cut surface of Wilms' tumor in the autopsy case showing variegated appearance 4c- External surface of Liver showing metastatic foci of Wilms' tumor4d- Tumor thrombus of Wilms' tumor located in the right atrium.

Discussion

Wilms' tumor is the most common renal tumor of childhood. Wilms' tumor accounts for 6% of pediatric malignancies and >95% of kidney tumors in children.[2]Most of the patients are found in the age group of 2 to 5 years like in our study. [3],[4] Wilms' tumor has been reported rarely as a congenital neoplasm and also in adults. Published Indian and asian literature have shown a male preponderance however our study showed otherwise [3],[4],[5],[6],[7] ,[8]The most common clinical presentation in our study was with an abdominal mass. These findings were consistent with study by Yao W et al.[8]There is no direct correlation of abnormal RFT with unilateral Wilms' tumor. Renal function tests were abnormal in one case only due to contralateral hydronephrosis. LDH is a non- specific tumor marker and raised levels signify rapid cell turnover rate and large tumor burden. The LDH activity was increased in a range of twofold to fourfold in all eleven patients. Our findings are consistent with findings by Liubimova NV et al.[9]USG and CT are accurate in diagnosing Wilms' tumor as seen in our study (70% and 68%). location. The accuracy is slightly higher than the study by Miniati D et al.[10]The importance of recording the weight of the specimen cannot be over emphasized. The latest protocol involves omission of adjuvant chemotherapy for young patients (<2 years) with small (<550 gms nephrectomy weight) COG stage I favorable histology Wilms' tumor provided lymph nodes are sampled and are free of tumor. Resection margins, renal sinus, renal capsule and lymph nodes have to be examined as lymph node involvement may upstage the pathological staging of the tumor. In our study, renal sinus involvement was seen in nine cases (Table1). Thus, we had very few cases belonging to Stage I. Also, dissimilar looking viable areas, small reddish areas (may represent blastemal component) and cystic change have to be documented and sampled. Cystic change could be a post chemotherapy change or the case may be a cystic partially differentiated Wilms' tumor, a dilemma which had occurred in one of our cases. Hence the information about neoadjuvant chemotherapy is very important. In case of a post – chemotherapy resection specimen, gridding of the tumor slice with diagrammatic documentation has to be done. This helps in objectively recording the percentage of viable tumor. This is of importance for deciding the postoperative chemotherapeutic regimen. Necrotic areas should not be excluded in these specimens.[11]The classic triphasic histology was seen in all 19 cases (excluding biopsies and postchemotherapy specimens-Table 2). Ours being a general hospital, not all patients were subjected to neoadjuvant chemotherapy. Hence, we could study specimens where the histology was not altered by chemotherapy. In a blastemal predominant Wilms' tumor, it may be difficult to differentiate it from other blue round cell tumors of childhood. In a mesenchymal predominant Wilms' tumor, congenital mesoblastic nephroma may enter the differential diagnosis. Correlation with the age of the patient and extensive search for other elements helps in diagnosis. Anaplasia which is the sole determinant of unfavorable histology was seen in one case only in our study (Table 2). Anaplasia/unfavourable histology has a poor prognosis, increased chances of recurrence and requires additional chemotherapeutic drugs (cyclophosphamide, etoposide) according to NWTS -5 regimen.[12] We had a rare variant of Wilms' tumor, the CPDN. The recognition of this entity is important due to the extremely good prognosis.[13] The reporting of nephrogenic rests in the nephrectomy specimens is important as they are forerunners of Wilms' tumor. This is especially useful in partial nephrectomies and for prediction of Wilms' tumor occurrence in the contralateral kidney.[14] We did not record nephrogenic rests in any of our specimens.

The neoadjuvant chemotherapy is given in order to arrest the tumor growth and shrink the tumor size which prevents intraoperative tumor spillage and rupture. SIOP recommends 4 weeks of chemotherapy prior to surgery. [15] These changes observed in eight cases of our study were consistent with those published in literature[16], [17]. The necrosis was predominantly seen in the blastemal component followed by the mesenchymal component and lastly the epithelial component. The percentage necrosis ranged between 40% to almost 90% in our cases. This correlated with the tumor response to chemotherapy. Presence of anaplasia also has to be recorded irrespective of chemotherapy.An unusual finding of an extensive cystic change post – chemotherapy was recorded. This diagnosis was initially thought to be CPDN. But after studying histology carefully, it was seen that the residual tumor within the septae had infiltrative and destructive margins as opposed to the pushing margins of a CPDN. Also, the diagnosis of CPDN was ruled out after correlating with pre operative radiology which suggested a solid tumor. This distinction was important due to the different prognosis of the two entities. This change represented extensive epithelial differentiation post chemotherapy. One has to be aware of this phenomenon post chemotherapy to avoid errors in tumor histology typing. Surgical difficulty was encountered in another postchemotherapy case where cartilaginous metaplasia was seen in the tumor thrombus within the inferior vena cava which was then difficult to milk out intraoperatively. Veno occlusive disease was observed in three cases, one autopsy and surgical case each which received chemotherapy, the third was an autopsy case who did not receive chemotherapy. Post chemotherapy differentiation of epithelial and mesenchymal components separately was observed in four out of seven cases in our study. It should be remembered that maturation of

immature components post chemotherapy does occur. But it is also important to realize that heterologous mature elements such as rhabdomyoblastic component or mature epithelial elements like squamous or mucinous may be unaltered by chemotherapy. Thus the importance of history of neoadjuvant chemotherapy.

To diagnose a Wilms' tumor on a biopsy is a challenge and has its own limitations. The reasons being that: i) All components may not be present in the biopsy. ii) A predominant blastemal population in the biopsy can mimic a neuroblastoma. iii) Mitosis may not be present. iv) Anaplasia if focal may not be included in the biopsy. Accurate diagnosis of Wilms' tumor was given in five cases only in our study. However, the need for biopsy diagnosis of Wilms' tumor is increasing nowadays due to the current protocol of neoadjuvant chemotherapy.Two of our cases had extension to the right atrium and also liver and lung metastasis. One of these cases succumbed to the illness before any treatment could be administered. The early recognition is important as Stage I tumor are treated with surgery alone whereas even for higher grade tumors good chemotherapeutic regimens are available.[18]

Conclusion

Wilms' tumor is a potentially curable tumor provided it is accurately diagnosed and properly staged. Multidisplinary meetings need to be encouraged for achieving appropriate management protocol. Appropriate treatment can be initiated only after vital inputs are received from the pathologists. Hence, we thought it is important to document our surgical pathology findings and share our experience.

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