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Case Series

Pathology Section

Exploring Wilms Tumour: A Series of Four Cases

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ABSTRACT

Wilms tumour, or nephroblastoma, is a common neoplasm in children, with a mean age of incidence between 2-5 years and no sex predilection. The incidence accounts for approximately 7.8 cases per million children, with bilaterality occurring in 5-10% of cases. This is a case series comprising four cases, each with a different histomorphological spectrum. Typically, Wilms tumour is a triphasic tumour comprised of blastemal, epithelial, and stromal components. This case series presents a variety of histomorphological spectra, including biphasic tumours with blastemal predominance, epithelial predominance, and stromal predominance with heterologous differentiation. These variations can aid in assessing the prognosis of the tumour. Usually, by immunohistochemistry (IHC), WT1 is positive in all Wilms tumours. However, in this case series, WT1-negative Wilms tumours are reported. Demonstrating unique cases with uncommon histological patterns and IHC markers can enhance our understanding of Wilms tumours and their management. This case series also aids in differentiating Wilms tumours from other paediatric renal tumours with similar histopathological patterns. Hereby, the authors present a case series of four children. The first case involved a one-and-a-half-year-old male child who presented with an abdominal mass that was noted incidentally in the right lumbar region after a self-fall within two weeks. The second case involved a six-year-old female child who presented with abdominal pain for one week following a fall, during which a mass was noted incidentally in the right hypochondrium upon clinical examination. The third case involved a two-year-old female child who also presented with an abdominal mass in the right hypochondrium for one month, which was discovered incidentally. The last case involved a three-year-old male child who presented with abdominal fullness for three days, and a mass was noted by the clinician in the left hypochondrium during clinical examination. All four children were diagnosed with Wilms tumour after radiological investigations and underwent 4-6 cycles of chemotherapy prior to radical nephroureterectomy. The resected specimens were received in the histopathological Department, and a diagnosis of Wilms tumour was made. An IHC panel was performed to rule out other small round blue cell tumours.

Keywords: Chemotherapy, Nephroblastoma, Nephroureterectomy

INTRODUCTION

Wilms tumour is a common paediatric renal neoplasm seen in the age group of 0 to 5 years, without any sex preponderance and with very few bilateral cases. Children can present with an abdominal mass, which is mostly asymptomatic and diagnosed incidentally. Haematuria and pain are rarely observed [1].

The majority of Wilms tumours are found to be sporadic. Approximately 10-15% of Wilms tumour cases are associated with syndromes like (Wilms tumour, Aniridia, Genital anomalies, Mental retardation (WAGR) syndrome, Denys-Drash syndrome (gonadal dysgenesis and early onset nephropathy), and Beckwith-Wiedemann syndrome. Deletion of the 11p13 chromosome band is observed in WAGR syndrome, while a germline mutation in the WT1 gene is noted in Denys-Drash syndrome. Beckwith-Wiedemann syndrome maps to 11p15. Dysregulation of Insulin-like Growth Factor II (IGF2) expression is the most common genetic alteration, found in the majority of sporadic Wilms tumours. WT1 mutated tumours show Catenin Beta 1 (CNNB1) mutations, and the majority of them show beta-catenin pathway activation. Mutations in the SIX1/SIX2 pathway and the DROSHA/ DiGreoge Syndrome Critical Region 8 (DGCR8) micro Ribonucleic Acid (RNA) microprocessor complex are found in high-risk blastemal Wilms tumours [2].

The pathogenesis of Wilms tumour comprises three components: IGF2 overexpression, dysregulated WNT signaling, and alterations in microRNA processing. A 1p/16q loss, 1q gain, and TP53 mutation are associated with disease progression and chemoresistance. Grossly, Wilms tumour presents as a large, solitary, well-circumscribed mass. Upon cutting open the specimen, a tumour is seen that is soft and grey-tan. Areas of haemorrhage, necrosis, and cyst formation may be noted. Microscopically, Wilms tumour exhibits triphasic histology composed of blastemal, epithelial, and stromal components. The blastemal cells are small, closely packed cells with a high nuclear-cytoplasmic ratio, round to oval nuclei, relatively inconspicuous nucleoli, and scant cytoplasm. The blastemal component is composed of the following differential patterns: diffuse, nested, serpentine, nodular, and basaloid patterns [3]. The serpentine blastemal pattern is the most distinctive. The diffuse blastemal pattern is responsive to molecular therapeutic protocols, thus remaining a favourable histological pattern. The epithelial pattern comprises cells resembling nephrogenesis with tubular, glomeruloid, papillary, and transitional patterns. It also includes heterologous cell types with mucinous, squamous, neural, and neuroendocrine cells. Tubular differentiation is the most frequent epithelial pattern. Stromal cells in Wilms tumour comprise myxoid, fibroblast, myofibroblast, smooth muscle, skeletal muscle, adipose cells, cartilage, osteoid, and neuroglial cells. Among these, tumours with skeletal muscle differentiation have a good prognosis. About 5% of Wilms tumours contain cells with large hyperchromatic nuclei and multipolar mitotic figures, indicating unfavorable histology. Wilms tumours lacking these features are designated as having favourable histology [4]. Here, authors present a case series of four children diagnosed and treated for Wilms tumour.

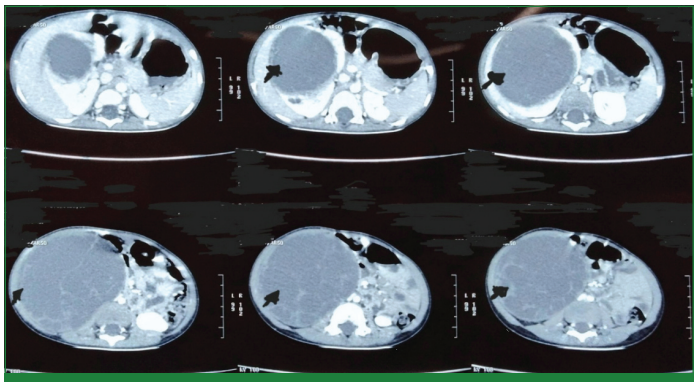
Case 1

A one-and-a-half-year-old male child presented to the Outpatient Department (OPD) with a history of a self-fall and sustained an injury to the right side of the abdomen. Following this, a swelling was noted in the right hypochondrium extending to the right lumbar

region two weeks ago. The swelling had an insidious onset and was gradually progressive, accompanied by a history of pain in the right lumbar region. The pain was dull, aching in nature, and non-radiating. There was no haematuria. On examination, a 7×5×4 cm well-defined mass was palpated over the right hypochondrium and lumbar region. The mass was firm in consistency, did not move with respiration, and was ballotable.

An Ultrasonogram (USG) of the abdomen was performed, revealing a well-defined heterogeneous lesion measuring 5.9 × 5.8 cm in the suprarenal region, which was compressing the right kidney. Focal caliectasis was noted in the lower pole. A differential diagnosis of Wilms tumour and neuroblastoma was suggested by the radiologist.

Subsequently, a Contrast-enhanced Computed Tomography (CECT) of the abdomen was performed, which showed a large heterogeneously enhancing mass lesion with cystic areas located in the anterior cortex of the upper and mid pole of the right kidney, along with focal caliectasis in the lower pole. There was no evidence of renal vein or inferior vena cava thrombus. The impression of Wilms tumour was given [Table/Fig-1]. The clinician proceeded to treat the patient with four cycles of neoadjuvant chemotherapy, consisting of vincristine and actinomycin D, and then performed a right nephrectomy.



[Table/Fig-1]: A mass lesion in the upper and middle pole (→) of kidney.

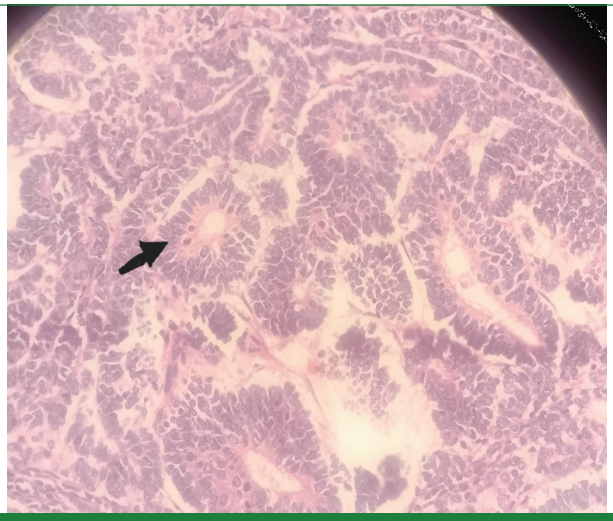
The resected specimen of the right kidney, along with the attached ureter and lymph nodes, was received in the Histopathological Department.

Gross examination revealed that the right kidney measured 12×10×3 cm, with an attached ureter measuring 6 cm in length. The external surface appeared bosselated, and there was no capsular breach. Upon sectioning, a mass measuring 9×6×3 cm was observed over the upper pole, surrounded by a thin rim of normal renal parenchyma. The mass appeared grey-white, firm, and homogeneous, with a few areas of necrosis. No haemorrhagic areas were identified.

Histological examination revealed renal parenchyma with a malignant neoplasm composed of triphasic elements, with the epithelial component constituting about 50%, the stromal components contributing around 40%, and the blastemal component accounting for approximately 10% [Table/Fig-2]. The tumour cells were arranged in lobules and nests, intermixed with malignant fascicles of spindle-shaped cells, elongated nuclei, and moderate cytoplasm. The renal sinus, renal hilum, renal capsule, perinephric fat, and ureter were free from tumour infiltration.

Sections studied from three lymph nodes showed features of reactive hyperplasia with sinus histiocytosis. A final impression of Wilms tumour (triphasic, epithelial predominant: 50%) was given, and a panel of Immunohistochemistry (IHC) was performed for confirmation.

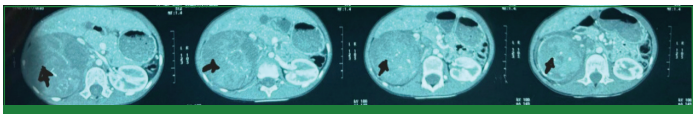
The WT1 was negative in tumour cells, Ki-67 showed nuclear positivity in less than 5% of tumour cells, and beta-catenin was found to be positive in tumour cells. Based on the histopathological reports, the child was started on postoperative chemotherapy with vincristine and actinomycin D. The child's health improved, and they were deemed fit for discharge.



[Table/Fig-2]: Section showing epithelial predominant Wilms tumour (H&E, 40x).

Case 2

A six-year-old female child presented with a history of abdominal pain for one week following a fall. There was no history of haematuria, weight loss, or loss of appetite. On examination, a mass was palpable in the right hypochondrium and right lumbar region, measuring 8×6×5 cm, which was firm in consistency and ballotable. A CECT abdomen was performed, which revealed a solid cystic lesion in the superior and middle pole of the right kidney, measuring 17.7×6.1×5.8 cm, with calcification and inferior vena cava displacement, not crossing the midline. Bilateral lung nodules were present. An impression of right Wilms tumour with lung metastases was provided in [Table/Fig-3]. The clinician started the child on six cycles of neoadjuvant chemotherapy with vincristine, actinomycin D, and doxorubicin, followed by right radical nephroureterectomy. The resected right kidney with lymph nodes was received in the Histopathology Department.

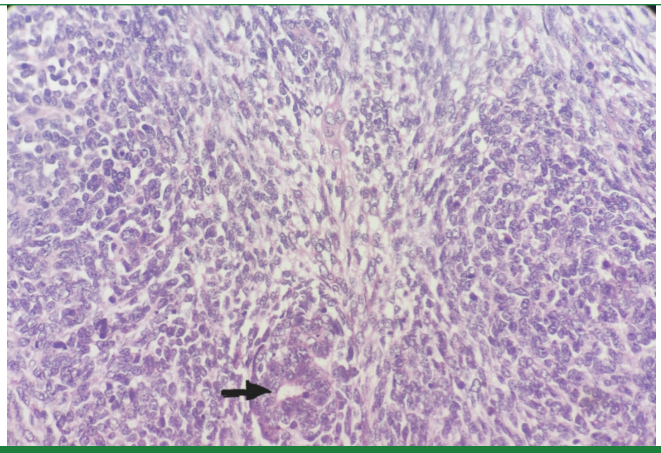


[Table/Fig-3]: Solid, cystic lesion in superior and middle pole of right kidney (→).

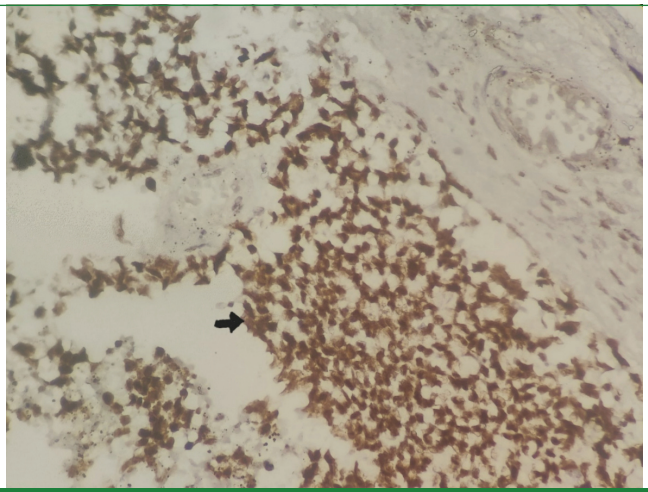
On gross examination, the right kidney weighed 165 grams, and the attached ureter measured 4 cm in length. The external surface showed an intact capsule. Upon sectioning the kidney, a variegated mass measuring 6.5×4.5×2 cm was observed in the superior and middle pole of the kidney, with necrosis present. The renal hilum, renal sinus, and ureter were free of tumour infiltration.

Microscopically, the section showed renal parenchyma with a neoplasm composed of cells arranged in sheets. The cells were small, round to oval, with hyperchromatic pleomorphic nuclei and inconspicuous nucleoli, with scant cytoplasm (blastemal) [Table/Fig-4]. Areas of hyalinisation and 50% necrosis were present. Some areas exhibited tumour cells arranged in syncytial clusters, while areas of fibrosis were also observed. Many foci displayed multinucleated giant cells. The capsule, renal hilum, renal sinus, ureter, and perinephric fat were free of tumour infiltration.

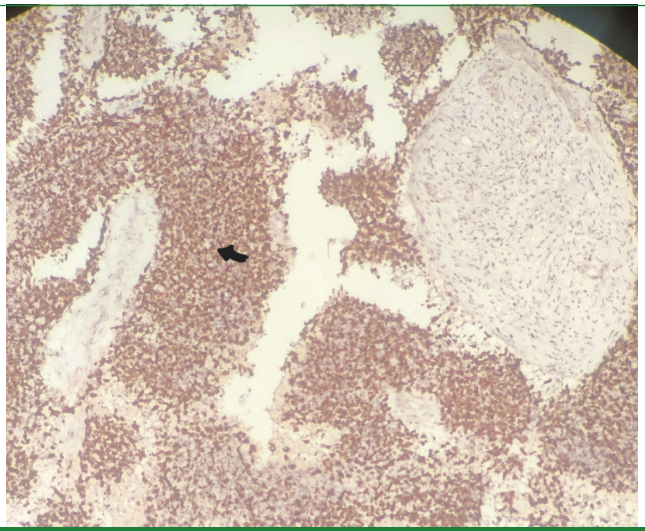
A panel of IHC was performed for confirmation. WT1 showed diffuse strong nuclear positivity in tumour cells [Table/Fig-5]. Beta-catenin was negative in tumour cells. Ki-67 demonstrated diffuse strong nuclear positivity in 70-80% of tumour cells [Table/Fig-6]. The final impression was Wilms tumour (biphasic) with post-chemotherapy changes. The blastemal component was identified in 70% of tumour cells, while the epithelial components were observed in 30% of tumour cells. Necrosis was present in approximately 50%, and the residual tumour covered 25-30%.



[Table/Fig-4]: Section showing neoplastic cells which are round to oval with hyperchromatic pleomorphic nuclei and inconspicuous nucleoli with scant cytoplasm (blastemal component) (→) with tubular component. (H&E, 40X).



[Table/Fig-5]: Section showing WT1 strong nuclear positivity (→) in tumour cells (IHC,40X).



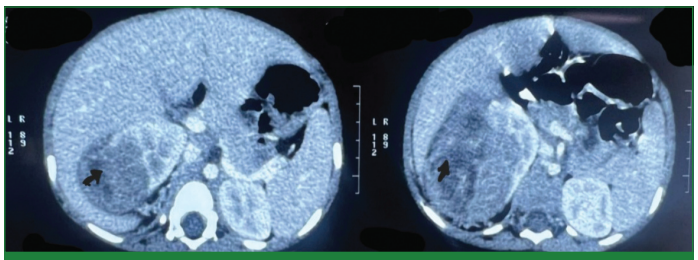
[Table/Fig-6]: Section showing Ki-67 diffuse strong nuclear positivity (→) (IHC,40x).

The child was started on postoperative chemotherapy with vincristine, actinomycin, and doxorubicin for six weeks. The lung metastatic site was treated with radiotherapy. The child was advised to follow a high-protein diet. Additionally, the child was informed about warning signs, including reduced urine output, abdominal distension, and breathlessness, and was instructed to visit the emergency room immediately if any warning signs arose.

Case 3

A two-year-old female child presented with complaints of a right-sided abdominal mass that had been noted incidentally while bathing for one month. The child had no history of vomiting or haematuria. Upon examination, a single firm mass measuring 10 × 8 cm was identified in the right hypochondrium, lumbar region, and iliac fossa. The mass was manually palpable. The patient was found to be hypertensive at the time of admission, with a recorded blood pressure of 140/100 mmHg, and was placed under continuous monitoring for elevated blood pressure. The hypertension was attributed to renin secretion by the tumour. Antihypertensives were initiated. The following differential diagnosis were considered by the clinician: foetal rhabdomyomatous nephroblastoma and Wilms tumour with skeletal muscle differentiation.

Positron Emission Tomography-Computed Tomography (PET-CT) was performed, revealing a metabolically active large retroperitoneal mass measuring 10.6×9.8 cm, which completely replaced the right kidney, encasing the right renal vessels and causing smooth indentation and displacement of adjacent structures [Table/Fig-7]. An initial impression of embryonal rhabdomyosarcoma was given. A trucut biopsy was conducted, which confirmed the diagnosis of Wilms tumour. The clinician initiated four cycles of neoadjuvant chemotherapy with vincristine and actinomycin and planned for a right radical nephroureterectomy. The specimen of the resected right kidney with ureter was subsequently received in the Histopathology Department.



[Table/Fig-7]: A mass replacing entire right kidney (→).

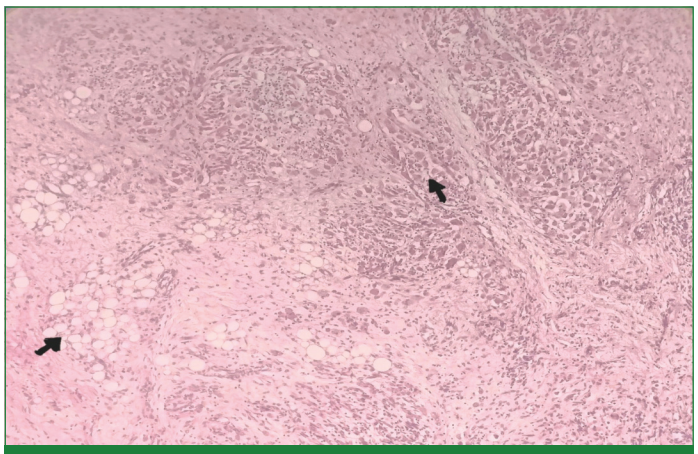
Grossly, the right kidney measured 12×10×8.5 cm, and the ureter measured 3 cm in length. Externally, the capsule remained intact. Upon sectioning the kidney, a large grey-white tumour replacing the entire kidney was observed. The mass measured 10×9×8.5 cm, with a peripheral thin rim of renal parenchyma. The kidney was predominantly solid, with focal xanthomatous and haemorrhagic areas, as well as multiple cystic areas in the periphery. The renal pelvis was filled with tumour.

Microscopically, the section studied showed a malignant neoplasm composed of small to medium-sized undifferentiated blastemal cells. The tumour contained 10% epithelial components in the form of malignant tubules and glomeruli, and 75% stromal mesenchyma composed of heterologous spindle-shaped rhabdomyoblastic differentiation with oval nuclei and abundant strap-like cytoplasm [Table/Fig-8]. A few areas also exhibited mononuclear inflammatory cells and xanthomatous changes within the malignant mesenchymal component. No significant anaplasia, atypical mitosis, necrosis, or haemorrhage were noted. A peripheral rim of thinned-out normal parenchyma was noted. Sections from the pelvicalyceal system showed tumour encroaching into the calyx. The renal hilum and renal pelvis had pads of fat involved by the tumour. Sections from subcapsular cystic areas also showed malignant tumour cell infiltration. Sections from the resected margins of the tumour exhibited normal histology, with no tumour cell infiltration noted.

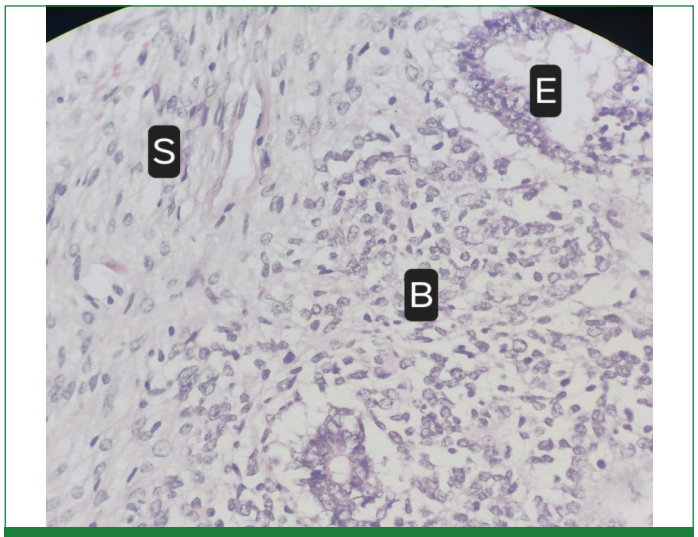
A panel of IHC was conducted to confirm Wilms tumour. WT1 was negative in muscle areas, while myogenin was positive in the skeletal muscle differentiation area. Beta-catenin showed variable positivity, with membrane positivity in malignant tubules and blastemal cells, as well as focal nuclear positivity in the blastemal area.

The Section showing Epithelial (E), Stromal (S) and Blastemal (B) component has been depicted in [Table/Fig-9]. The final impression after IHC was suggestive of WT1-negative Wilms tumour with heterologous skeletal muscle differentiation. The patient was started

on four cycles of postoperative chemotherapy with vincristine and actinomycin. Medications for hypertension were administered, and the patient was discharged.



[Table/Fig-8]: Section showing spindle shaped rhabdomyoblastic differentiation (→) of Wilms tumour (H&E, 40x).



[Table/Fig-9]: Section showing Epithelial (E), Stromal (S) and Blastemal (B) component (H&E, 40x).

Case 4

A three-year-old male child was brought to the hospital with a history of abdominal fullness in the left lower abdomen for three days. On examination, a mass was observed over the left hypochondrium, lumbar region, and iliac fossa, extending from 2 cm below the left costal margin to 2 cm above the anterior iliac spine, which was firm to hard in consistency.

A CT scan of the abdomen revealed a well-defined iso- to hypodense lesion measuring 11.1×7.6×7 cm in the mid to lower pole of the left kidney. The patient was diagnosed with Wilms tumour in the left kidney. The child was started on four cycles of neoadjuvant chemotherapy with vincristine and actinomycin. A left radical nephroureterectomy was performed, and the resected specimen was sent to the histopathology department.

Grossly, the received nephrectomy specimen weighed 400 grams and contained an attached mass measuring 14×9×5 cm. The external surface appeared congested. Upon sectioning, normal parenchyma measuring 4×3.5×1 cm was identified, with an attached tumour occupying the lower pole of the kidney, measuring 9×7×3 cm. Areas of haemorrhage and necrosis were noted.

Microscopically, the section showed renal parenchyma with a neoplasm arranged in a triphasic pattern composed of blastemal, epithelial, and stromal components. The blastemal components consisted of cells arranged in nests, cords, and sheets. The cells had small, round, pleomorphic nuclei with scant cytoplasm. The epithelial component was composed of cells arranged in tubules. The stromal component was composed of elongated spindle cells with moderate eosinophilic cytoplasm, alongside areas of necrosis and haemorrhage. No anaplasia was noted. The capsule, vascular margin, ureteric margin, and renal sinus were free of tumour infiltration.

The WT1 was found to be negative in the tumour cells, while beta-catenin was found to be positive in the tumour cells. Ki-67 showed nuclear positivity in 5-10% of the tumour cells. A final impression of Wilms tumour (triphasic) was made, with the blastemal component constituting 40%, the epithelial component contributing 30%, and the stromal component accounting for about 30%was made after confirmation with IHC.

The child was started on five cycles of postoperative chemotherapy with vincristine and actinomycin, along with radiotherapy. The child was given dietary advice and was discharged as the condition improved.

DISCUSSION

Nephroblastoma, also known as Wilms tumour, is an embryonic tumour that contains mesenchymal and rudimentary renal epithelial cells. Numerous congenital anomalies, including aniridia, hemihypertrophy, hypospadias, polycystic kidney disease, and horseshoe kidneys, are linked to Wilms tumour [1]. Most patients are asymptomatic [3]. Some may present with an abdominal mass on palpation, which is the most common presentation [4]. Others may present with haematuria and hypertension [5]. Wilms tumours in children and adults are similar in terms of histology and radiology [6] and are made up of stromal, blastemal, and epithelial components. The most common histopathological pattern is triphasic, followed by the blastemal predominant pattern [7]. The variant with blastemal predominance is more aggressive [8]. The stromal and epithelial forms have a moderate level of increased risk [9]. Both histologically and clinically, all paediatric kidney neoplasms are identical, and prognosis is assessed by the histopathological staging of Wilms tumour. Hence, the pathologist finds it challenging to diagnose a case of Wilms tumour due to similar histological patterns and varying subtypes. Here, molecular diagnostics and IHC panel aid in accurate diagnosis and confirmation of Wilms tumour. Among these, WT1 is the most sensitive marker. However, due to the high number of driver mutations in WT1, molecular testing is neither sensitive nor selective.

Children under two years of age generally have a good prognosis, as metastasis and anaplasia are rare. Extensive tubular differentiation and skeletal muscle differentiation are also considered good prognostic factors. Wilms tumours with poor prognoses are noted under the following conditions: increased size of the tumour with invasion into the renal capsule, renal sinus, and intrarenal vessels. Mutations of the Tp53 gene and loss of heterozygosity at 1p and 16q are also considered poor prognostic factors. Therefore, children in the younger age group (under two years) and those with locally spreading tumours tend to have better survival rates. Poor survival is observed in children with late presentations due to inadequate care, treatment abandonment, delayed surgery, metastatic disease, and unfavourable histological subtypes.

The International Society of Paediatric Oncology (SIOP) recommends preoperative chemotherapy. The chemotherapy regimen for unilateral tumours consists of four weeks of treatment with vincristine (administered weekly) and actinomycin D (administered biweekly). For bilateral cases, vincristine, actinomycin D, and doxorubicin are given for no longer than 9 to 12 weeks. For metastatic Wilms tumour, vincristine, actinomycin D, and doxorubicin are administered for 6 weeks. Postoperative chemotherapy is given to all patients except those with low-risk

Authors name and year of the study	Age/sex	Clinical feature	Size and site of lesion	Radiology findings	Histopathological findings	IHC
Rathod G and Shah K, 2017 [11]	3 years/ male	Swelling in left side of abdomen for 1month. Hypertension present.	5×4 cm	Solid mass with cystic areas measuring 7.5×5.3 cm on lower and upper quadrant arising from left kidney.	Triphasic- blastemal, stromal and epithelial tubular formation with immature glomeruli	-
Hermi A et al., 2022 [12]	26 year/ male	Right flank pain ×12 month. Gross haematuria present.	No palpable mass	Upper pole of right renal mass measuring 73×69×62 mm, well encapsulated, blending to inferior surface of liver.	Biphasic-blastemal, epithelial differentiation with pseudo rosettes	Positive for WT1,CD56, Ki-67- 40%
Qu Y-N et al., 2022 [13]	6 month/ male	Right cryptorchidism after birth. Mass in lower abdomen, hepatomegaly, cardiomegaly, hypertension	-	Homogenous soft tissue mass measuring 48.7x49.5x52.8 mm with ascites, bilateral pleural effusion	Triphasic- stromal, epithelial, renal blastemal elements within tumour	WT1, EGFR, CK19, AE1/AE3,CAM5.2 positivity.
Chan GJ et al., 2024 [14]	31 year/ female	Left renal mass in 2010, underwent resection. Pathology report unknown. Now came with hepatic lesion with metastatic appearance	-	-	Triphasic pattern- tubular structure, immature blastemal component, mesenchymal component	Positive for CK (AE1/ AE3), WT1, BCL2, CD56.
Bajaj S et al., 2022 [15]	39 year/ female	Right abdominal pain and fullness for 2 weeks	Palpable fullness adjacent to liver, non tender	Large, solid mass measuring upto 12.6 cm in inferior pole of kidney	Triphasic component- blastemal, stromal, epithelial components. Blastemal component involves primitive small round blue cells with scant cytoplasm and rapid mitotic activity	-
Case-1	1 1/2/ male	Swelling in right lumbar region	7×5×4 cm	Heterogenously enhancing mass lesion in upper and mid pole of right kidney	Triphasic component with epithelial predominance	WT1-negative Ki-67-<5% positive beta-catenin-negative
Case-2	6 year/ female	Abdominal pain for 1 week after a self-fall	8×6×5 cm	Solid, cystic lesion in superior and midpole of right kidney	Biphasic Wilmstumour with post chemotherapy changes	WT1- diffuse strong nuclear positivity. Ki-67- diffuse strong nuclear positivity in 70-80% tumour cells. Beta-catenin-negative
Case-3	2 year/ female	Right abdominal mass for 1 month	10×8 cm	Retroperitoneal mass replacing entire kidney	WT1 negative Wilmstumour with heterologous skeletal muscle differentiation.	WT1- negative Myogenin-positive Beta – catenin-variable positivity.
Case 4	3 year/ male	Abdominal fullness in left lower abdomen	2 cm below left costal margin to 2 cm above anterior superior iliac spine	Lesion in mid to lower pole of left kidney	Triphasic Wilms tumour	WT1- negative Beta-catenin-positive Ki-67-5-10% positivity

[Table/Fig-10]: Comparison of published literature with present cases [11-15].
EGFR: Epidermal growth factor receptor: CK; Cytokeratin: CAM; Cytokeratin adhesion molecule

tumours. Postoperative radiation is provided for patients with intermediate and high risk. Pulmonary radiation is administered for patients with lung metastasis [10].

The differential diagnosis of Wilms tumour includes the following: Blastemal predominant Wilms tumour resembles other small blue cell tumours of childhood, namely neuroblastoma and Ewing sarcoma. These small blue cell tumours can be differentiated from Wilms tumour by immunohistochemical markers. Very rarely, electron microscopy, molecular diagnostic techniques, and cytogenetics may be required to confirm the nature of the small blue cell tumour. Epithelial predominant Wilms tumour resembles papillary renal cell carcinoma, metanephric adenoma, and clear cell renal cell carcinoma. These can be differentiated from Wilms tumour by immunohistochemical staining, molecular techniques, and diagnostic techniques. Stromal predominant Wilms tumour resembles congenital mesoblastic nephroma, the spindle cell variant of clear cell sarcoma, and synovial sarcoma. The Comparison of published literature with present cases has been depicted in [Table/Fig-10] [11-15].

CONCLUSION(S)

Wilms tumour is the most common neoplasm of the kidney in the paediatric age group. Most cases are diagnosed incidentally. Wilms tumour is confirmed radiologically and histopathologically with IHC. A child with Wilms tumour has been treated with nephrectomy, chemotherapy, and radiotherapy. Early diagnosis and treatment of Wilms tumour are associated with a good prognosis.

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