

## Case Report

# Pure epithelial wilms' tumor in a 57-year-old patient: a case report and literature review

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**Abstract:** Background: Wilms' tumor (WT) is the most common, malignant kidney tumor in children, but it rarely occurs in adults. Few studies have reported WT patients of over 50 years of age. In this case report, we present a special case of a 57-year-old female patient diagnosed with pure epithelial WT. The CT scan demonstrated a heterogeneously enhanced mass in the upper pole of the left kidney. Then the patient underwent a left radical nephrectomy and a regional lymph node dissection for treatment. Gross observations revealed two masses adjacently located in the parenchyma of the kidney. Microscopically, the tumors were comprised of monomorphic epithelial cells arranged in the tubulopapillary region, small nests, adenoid and ribbon-like patterns. Furthermore, the tumor cells were crowded and uniform with pale chromatin containing sparse and basophilic cytoplasm. Moreover, the tumor cells were immunoreactive for WT-1, PAX-2, PAX-8, CAM5.2, CD56, CyclinD1,  $\beta$ -catenin, and E-cadherin, but negative for CD10, GATA3, CAIX, Vim, CK7, P53, P504S, CD117, NapsinA, CDX-2, Villin, S-100, CK20, CEA, ER and EGFR. The patient was finally diagnosed with pure epithelial WT. The patient did not receive additional treatment except for the surgical resection. No evidence of recurrence was observed during the 6-month follow-up period. Adult WT is a rare and highly malignant tumor, and an accurate diagnosis is difficult when typical triphasic histological patterns are absent. The use of a specific immunohistochemical marker panel can help reach an accurate diagnosis.

**Keywords:** Wilms' tumor, pathological diagnosis, immunohistochemistry

## Introduction

Wilms' tumor (WT) is rarely reported in adult individuals, which causes difficulties in the diagnosis and treatment of this tumor in adults [1]. To the best of our knowledge, only a few reports of adult WT have been previously published [2-11] (**Table 1**). Owing to the low incidence rate of WT in adults, the pathological features of adult WT have been rarely studied. In a study reporting on 11 cases of adult WT that were similar to pediatric cases, a classic triphasic pattern (including blastemal, epithelial, and mesenchymal components) was observed in seven (66%) cases, and a biphasic pattern was observed in four (34%) cases [12]. In the present study, we report a 57-year-old female case, who is the oldest patient with WT, to date. Pathologically, the tumor exclusively consisted of epithelial cells. In view of its high malignancy and low incidence in adults, the

pathological diagnosis with only one component for WT is difficult and can be easily missed. An accurate classification for this kind of tumor is crucial for both therapeutic intervention and prognosis.

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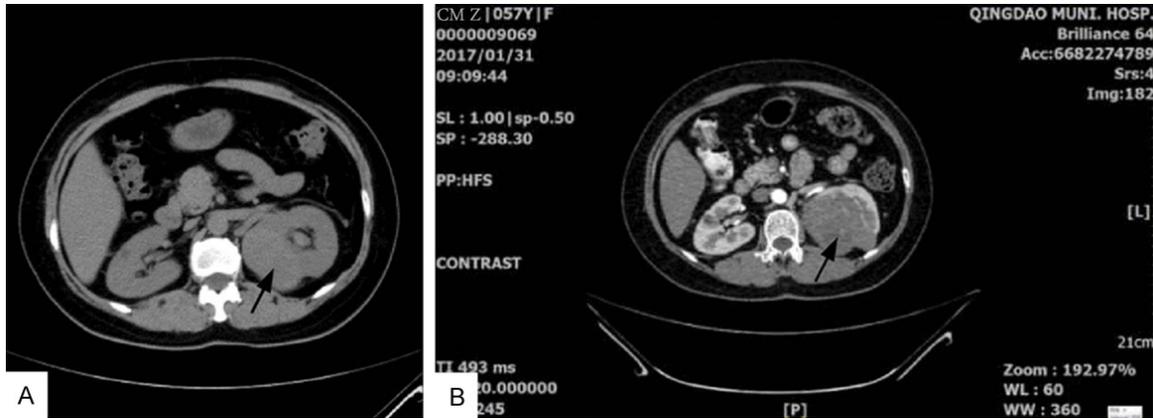
A 57-year-old woman visited the Department of Urology of Qingdao Municipal Hospital due to hematuria for a week. The CT scan demonstrated a heterogeneously enhanced mass in the upper pole of the left kidney (**Figure 1**). The patient underwent a left radical nephrectomy and a regional lymph node dissection for treatment.

Gross observations revealed that the two masses were adjacently located at the upper pole of the kidney, in which one was colorful, while the other was grey/white (**Figure 2A**). These masses were 5.5 cm and 2.5 cm in diam-

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**Table 1.** Reported cases of adult Wilms' tumor

First author/Ref	Year	Age (year), gender	Main complaints	Size (cm)	Microscopic characteristics	IHC staining	Outcomes
1 Masuda [2]	2004	22, male	Right flank pain	4.2×1.8	Predominantly epithelial histology	No description	No recurrence at 15-months follow-up
2 Varma [3]	2006	48, male	Flank pain and hematuria	11×10	Highly cellular, comprising epithelial, blastemal and stromal elements	No description	No recurrence at 8-months follow-up
3 Thevendran [4]	2010	37, female	Left flank mass	9.5×14.2	Triphasic pattern composed of epithelial, blastemal and stromal elements	WT1+	She underwent a radical nephrectomy and was receiving chemotherapy.
4 Guo [5]	2011	54, male	Low backache and colicky left loin pain	2.5×2.3	Triphasic pattern of blastemal, epithelial, and stromal components	WT1+	Multiple metastases to the liver, lung, and chest wall at 12 months, and died.
5 Patnayak [6]	2012	19, male	Low backache	15×10	Monomorphous tumor cells presenting as nests, islands and sheets, with necrosis and lymphoid collections	S100+, CD117+,NSE+	Lost to follow-up
6 Seifert [7]	2012	26, female	Fever	12	Primarily undifferentiated blastemal cells	PANCK+, Vimentin+	Remarkable improvement in lung metastases
7 Morabito [8]	2014	38, male	Abdominal pain and macroscopic hematuria	10	Triphasic cellular pattern with undifferentiated blastemal cells and cells differentiating toward epithelial and stromal lineages	Vimentin+, Desmin+, WT1+	Alive and free of disease progression at 6-months follow-up
8 Longwen [9]	2014	25, female	Back pain and urinary tract infection	No description	Predominantly epithelial histology	WT1+	Free of disease progression at 3-years follow-up
9 Huang [10]	2015	20, female	Left flank pain and back pain	6.4×6.2	Triphasic pattern of blastemal, epithelial and stromal components	Vimentin+, CD99+, CD117+, WT1+	No recurrence at 12-months follow-up
10 Jia [11]	2015	51, male	A mass without clinical symptoms Identified by check-up examination	4.0×4.5	Undifferentiated blastemal cells differentiating to various degrees and epithelial and stromal lineages in different proportions	WT1+	No recurrence at 2-years follow-up
11 Present	2016	57, female	Hematuria	5.5×5.5 and 2.5×2.5	Pure epithelial cells	WT-1+, Pax-8+, CD56+	No recurrence at 6-months follow-up



**Figure 1.** A computed tomography (CT) scan of the kidneys. A. The non-contrast-enhanced CT scan revealed a round, hypodense mass (38HU), with a size of 6.9×7.6 cm, in the upper pole of the left kidney. B. The contrast-enhanced CT scans revealed the heterogeneous enhancement pattern (59 HU) of the mass, with unclear boundaries and patchy calcification (indicated by arrows).

eter, respectively. Microscopically, both tumors had a thick fibrous capsule and multifocal capsule invasion (**Figure 2B**). Both tumors were comprised of monomorphic epithelial cells. Massive necrosis and hemorrhage were observed in the large tumor, which had complex structures with tumor cells arranged in the tubulopapillary area, small nests, adenoids, and ribbon-like patterns (**Figure 2C**). The structural patterns of the small tumor were mainly small nests, adenoid, and ribbon-like. The low columnar-shaped tumor cells were crowded and uniform with pale chromatin. Part of these short fusiform or ovoid cells had little nucleoli. The cytoplasm was sparse and basophilic, and some of the tumor cells had apocrine. Nuclear fissions were rare and stromal elements were absent. The histocytes were clustered in the large fibrous vessel axis (**Figure 2D**). The tumor cells were immunoreactive for WT-1 (**Figure 2E**), PAX-2, PAX-8 (**Figure 2F**), CAM5.2, CD56, CyclinD1,  $\beta$ -catenin and E-cadherin, but not for CD10, GATA3, CAIX, Vim, CK7, P53, P504S, CD117, NapsinA, CDX-2, Villin, S-100, CK20, CEA, ER and EGFR. The mean Ki-67 proliferation index of the tumor was 30%. Combining the histopathological features and immunostaining results, the patient was diagnosed with WT of a differentiated type (pure epithelial WT). The patient did not receive additional treatment except for surgical resection. No evidence of recurrence was observed during the 6-month follow-up period. In addition, the patient did not re-visit our hospital on schedule a year later.

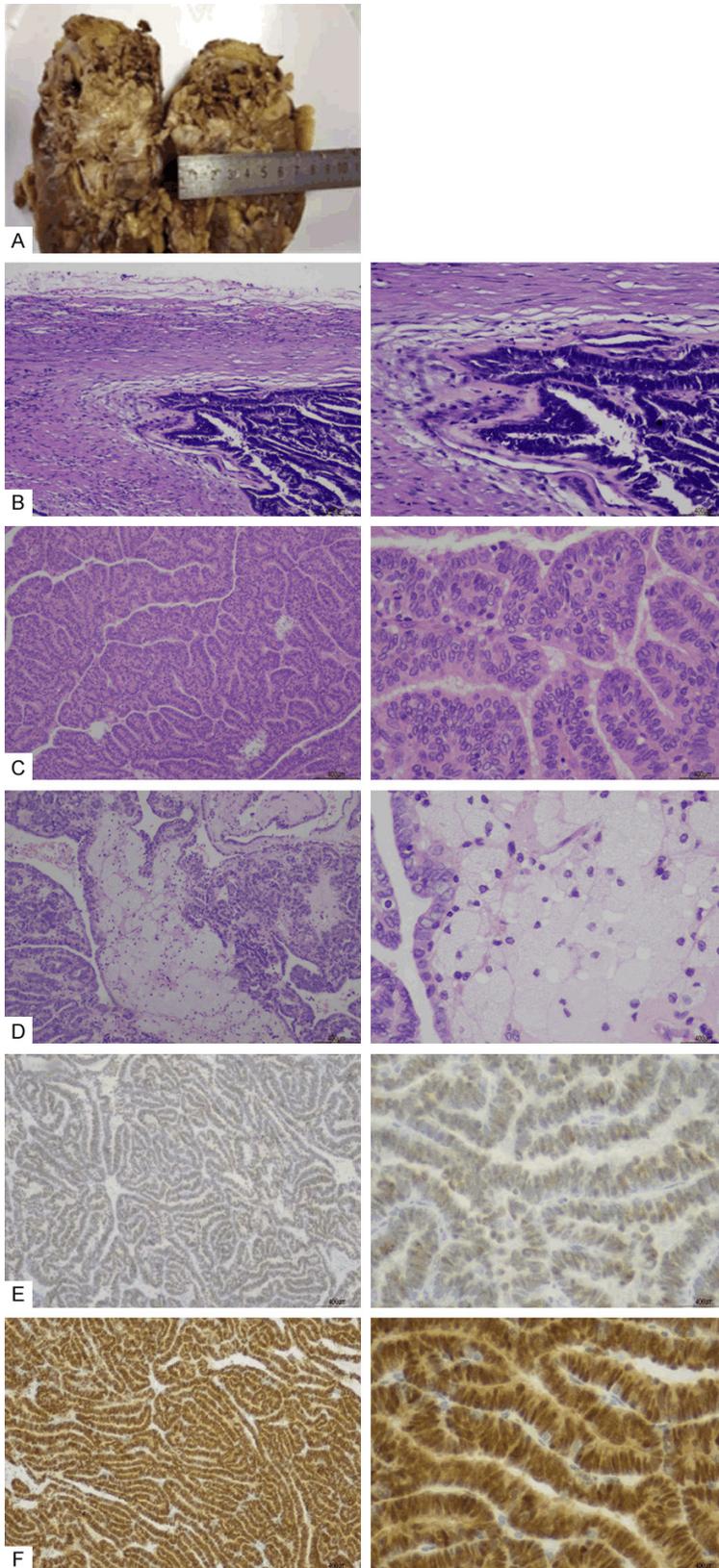
## Discussion

WT, also known as nephroblastoma, is a prototype of tumor formation at the morphological and molecular level, which occurs during embryonic development. Just 3% of WT are reported in adult individuals older than 16, without gender differences [1]. Given its remarkably low incidence, there are no specific guidelines for adult WT, resulting in misdiagnosis or missed diagnosis, as well as improper treatment. To date, adult WT is treated according to therapeutic protocols from the pediatric National Wilms' Tumor Study Group (NWTs) data. Jonathan *et al.* studied 128 adult patients with WT and found that adult WT was less sensitive to treatment and had a poorer prognosis than pediatric WT [13]. Unlike pediatric WTs, which are mainly asymptomatic and present with an abdominal palpable mass, the major symptoms of adult WTs are painless hematuria and local pain.

## Histology

Histopathologically, there is no difference between adult and pediatric WT, with a classic triphasic pattern that includes blastemal elements, primitive mesenchymal stroma and primitive epithelia. To date, WT with only one or two components is relatively rare. The present study reports an adult WT case that was comprised of pure epithelial cells, with the histological patterns of ribbons, adenoids, papillae and small nests. Like the present case, Chen *et al.*

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**Figure 2.** Pure epithelial Wilms' tumor in an adult patient. (A) Two adjacent cystic masses were observed in the upper pole of the left kidney. (B) The tumor had a thick fibrous and multifocally invaded capsule. (C) The tumor

cells formed complex structures with low columnar cells. (D) Histo-cytes were clustered in the large fibrous vessel axis. Tumor cells were immunoreactive for WT-1 (E) and PAX-8 (F). Magnification for micro-scopic images: left panel, 100×; right panel, 400×.

[9] reported an adult WT case that was predominantly epithelial cells with tubule, gland, and papilla structures. In this case, some cells had apocrine secretions. This was probably because the WT cells are primitive cells, which can differentiate into various kinds of epithelial cells, such as ciliated epithelia, mucous epithelia, squamous epithelia and urinary tract epithelia, as well as a variety of endocrine cells and nerve, fat, bone and cartilage, and hematopoietic tissue. Therefore, the major differential diagnosis was teratoma. In this case, the epithelial cells exhibited a primitive morphology. The present findings revealed a high Ki-67 proliferation index (30%) and low mitosis, suggesting a robust proliferative activity of the tumor.

### *Differential diagnosis*

In the present case, the tumors presented with complex histological structures that were comprised of monotonous epithelial cells. The tumors should be differentially diagnosed with solid papillary renal cell carcinoma (s-PRCC), metanephric adenoma (MA), neuroendocrine tumor and metastatic adenocarcinoma. In particularly challenging cases, the use of immunohistochemical markers can aid in the accurate diagnosis of WT.

Microscopically, WT and s-PRCC exhibit significant similarities. Both of these comprise

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monomorphic epithelial cells, are encapsulated by a well-circumscribed, thick, and fibrous capsule. In addition, some adult WTs have papillary patterns with foam cells gathered in the stroma, which is similar to s-PRCC. Immunohistochemically, s-PRCC is positive for CK7, CD15, and AMACR, but negative for CD56, and WT-1, which is different from WT.

MA is a type of tumor remarkably similar to WT, with regard to both morphological and immunohistochemical characteristics. Some investigators have even considered that MA is a well-differentiated nephroblastoma (post-renal residuals). MA is a benign tumor derived from metanephric blastema. Grossly, it is unifocal, well-circumscribed and non-encapsulated with a sharp tumor/normal interface. Microscopically, it lacks a pseudocapsule in the majority of cases. The tumor forms a sharp interface with the non-neoplastic kidney parenchyma. Typically, MA are comprised of tightly packed small and uniform cells with a scanty cytoplasm, in which the neoplastic cells are arranged in solid sheets or in small acini-like aggregates and form a retiform or ill-defined tubular pattern. The stroma is often inconspicuous but is sometimes hyalinized or edematous [14]. Immunohistochemically, both tumors are positive for WT-1, PAX-2, and PAX-8. However, most WTs are positively immunoreactive to WT-1, and CD56 and negatively immunoreactive to CD57, CK7, and AE1/3. In contrast, positive staining with WT-1, CD57, CK7 (focal), and AE1/3 (focal), and negative for CD56 strongly favors the diagnosis of MA. In the present case, tumor cells infiltrated the surrounding tissues, which suggest the malignant biological behaviors. With these immunohistochemical findings, the patient was diagnosed with WT.

The microscopical pattern of a neuroendocrine tumor is solely with the cells, which are usually arranged in a ribbon structure. In the immunohistochemical staining, the tumor cells were positive for CD56. The case in the present study lacked a classic "pepper-salt" morphology of nuclei with a fine granular chromatin in pathology. In addition, the case had negatively expressed specific neuroendocrine markers, such as CgA, Syn, and NSE.

In the present case, a differential diagnosis from metastatic adenocarcinoma, such as endometrial adenocarcinoma and gastrointestinal adenocarcinoma, should be considered.

The present patient underwent uterine resection for treating pathology-confirmed uterine fibroids five years ago. Moreover, tumor cells did not express the specific biomarkers for endometrial adenocarcinoma (e.g. ER, CK and Vim) or gastrointestinal adenocarcinoma (e.g. CDX-2, Villin and CK20), which hardly support the metastasis of these carcinomas.

### *Genetic characteristics*

WT has been generally considered to arise from nephrogenic rests (i.e. embryonic tissue) derived from the metanephric mesenchyme during renal development. The genetic aberrations underlying this process are known to be heterogeneous and include the inactivating mutations of the WT1 gene, which is localized to a specific region of chromosome 11p13. The sequence analysis demonstrated that 11p13 acts as a transcriptional regulator, whose protein product significantly affects specific DNA motifs [15]. The WT suppressor gene (WT1) encodes a zinc finger transcription factor, WT1, which has been implicated in various cellular processes, including proliferation, differentiation, and apoptosis. However, the precise role of the WT1 protein remains unknown. Recent research has demonstrated that Wnt/ $\beta$ -Catenin is activated in a chemically induced rat model of WT [16]. Indeed, there is evidence of the activation of the canonical Wnt/ $\beta$ -catenin pathway in up to 75% of WTs with WT1 mutations, and some studies have suggested that more than half of all WTs show Wnt activation [17-19]. Peter *et al.* [20] described a transgenic mouse model of primitive renal epithelial neoplasms that had high penetrance and mimicked the epithelial component of human WT. They found that the introduction of a stabilizing  $\beta$ -catenin mutation restricted to the kidney was sufficient to induce primitive renal epithelial tumors. However, when compounded with the activation of K-RAS, mice developed large, bilateral, metastatic, and multifocal primitive renal epithelial tumors that had the histologic and staining characteristics of the epithelial component of human WT.  $\beta$ -catenin is an important component of the Wnt signaling pathway that causes tumor growth through the activation of its downstream target genes, such as C-myc, survivin, and cyclinD1. In the present case, the tumor cells positively expressed E-cadherin,  $\beta$ -catenin, and cyclinD1, suggesting the activation of the wnt/ $\beta$ -catenin signaling pathway in the occurrence and development of this tumor.

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Signaling pathways mediated by tyrosine kinase receptors in response to growth factors, such as insulin-like growth factor-I (IGF-I), epidermal growth factors (EGF), and vascular endothelial growth factor (VEGF), have also been implicated in WT pathogenesis [21-24]. Ras comprises of a family of GTP-dependent proteins (G-proteins) that are located at the inner surface of the cell membrane. These membrane-bound G-protein-coupled receptors play a critical role in the activation of a series of their downstream signaling cascades, including the mitogen-activated protein kinase (MAPK) pathway and the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) pathway. Previous evidence has shown that the simultaneous activation of K-RAS and  $\beta$ -catenin in a developing nephron increased the number and size of WT and induced distant metastases [20]. K-RAS is one of the most frequently mutated human oncogenes in various cancers. In some settings, oncogenic K-RAS can trigger cellular senescence, whereas in others, it produces hyperproliferation. Elucidating the mechanisms that regulate these two drastically distinct outcomes would help to identify novel therapeutic approaches in RAS-driven cancers. In a previous study, using a combination of functional genomics and mouse genetics, Vicent *et al.* [16] found that WT1 is essential for regulating the senescence and proliferation downstream of oncogenic K-RAS signaling. These findings reveal important mechanisms for K-RAS-induced oncogenesis, in which WT1 was the key regulator of the genetic network of oncogenic K-RAS.

### Therapy and prognosis

Pediatric WT arises from pluripotent stem cells, rendering it sensitive to chemotherapy. In contrast, renal neoplasms in adults usually originate from renal tubules, making these less sensitive to chemotherapy. Therefore, it is imperative for adult WT patients to develop an individualized treatment strategy, such as gene targeting therapy. For instance, targeting for CD56, a nerve cell adhesion molecule, may represent a feasible adjunctive treatment for patients with WT. Vicent *et al.* [25] reported the identification of WT1 as a K-RAS synthetic-lethal gene in a mouse model of lung adenocarcinoma. Given that K-RAS is frequently mutated in human cancers, it may represent an in-

triguing and promising therapeutic target for WT. However, direct attempts to target activated Ras proteins have faced many obstacles. Therefore, recent studies have focused on identifying indirect targets to inhibit Ras-induced oncogenesis [26]. In a study conducted by Pinthus *et al.* [24], ErbB2 was identified as a tumor-associated antigen and a suitable therapeutic target for WT.

With proper treatment, including systematic chemotherapy, surgery and others, most cases of WT (80-90%) have a good prognosis. Furthermore, the size of the tumor is positively correlated to the prognosis. Histologically, rhabdoid and glomeruloid differentiation indicate a good prognosis, but mucus composition reveals a poor prognosis [27]. Somatic deletion in the long arm of the chromosome 16 (16q) is known to predict aggressive tumor phenotypes and unfavorable outcomes in WT, such as diffuse anaplasia, high-stage disease, and even death [14].

### Conclusion

Adult WT is a rare and highly malignant tumor, and obtaining an accurate diagnosis is difficult when the typical triphasic histological pattern is absent. A differential diagnosis is crucial for both therapeutic intervention and prognosis prediction. The use of specific immunohistochemical markers can help to reach an accurate diagnosis. To date, several molecular prognostic factors have been identified. The development of novel treatment, particularly with personalized gene-targeted therapy, is necessary.

### Disclosure of conflict of interest

None.

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