doi: 10.5146/tjpath.2016.01363

Teratoid Wilms Tumor: Report of Three Cases and Review of the Literature

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ABSTRACT

Teratoid Wilms tumor is a rare variant of Wilms tumor composed predominantly of well-differentiated epithelial and/or mesenchymal heterologous elements. Like the classical Wilms tumor, this variant may also occur as a renal mass or may be found in extra renal locations. This tumor may be treated effectively by surgical resection; however, it generally fails to respond to chemotherapy. A review of the literature revealed 30 reported cases of intra renal and 5 reports of extra renal teratoid Wilms tumor. We report our experience with an additional three cases of renal teratoid Wilms tumor adding to the 30 cases previously reported.

Key Words: Wilms tumor, Teratoid, Extrarenal, Kidney

INTRODUCTION

Wilms tumor (WT) is the most commonly diagnosed neoplasm of the kidney in children less than ten years of age. It is an embryologic tumor that histologically mimics renal embryogenesis and is composed of a variable mixture of stromal, blastemal, and epithelial elements (1-3). Teratoid Wilms Tumor (TWT) is a rare variant characterized by predominance of heterologous elements in addition to classic WT components. Tumors of this type behave differently compared to the usual WT because they generally do not respond to chemotherapy or radiation but may be treated effectively by surgery alone (4,5).

In this paper we present three cases of TWT and correlate our findings with a brief review of literature.

CASE REPORTS

Case 1: A two-year-old male presented with abdominal distension for two months due to a large abdominal mass. An abdominal CT scan revealed large heterogeneous soft tissue mass in the posterior aspect of the right kidney, measuring 18 x10 x 7 cm and extending beyond the renal cortex but not crossing the midline (Figure 1A). The patient underwent right nephrectomy. The nephrectomy specimen weighed 636 g with the outer surface distorted by coarse nodularity. The cut surface revealed extensive replacement of renal parenchyma by a variegated greyish white, partly cystic 15 x 8 x 6 cm mass with large areas of necrosis. A thin rim of unremarkable renal parenchyma was identified at the periphery of the mass (Figure 1B). On microscopic examination, approximately 90% of the tumor was composed of rhabdomyomatous elements (Figure 1C-E). In addition there were multiple foci of squamous epithelium and mature adipose tissue. Blastemal elements were identified in a few areas. The tumor extended beyond the capsule and infiltrated the renal sinus adipose tissue. No anaplasia was detected. Hilar lymph nodes were free of tumor. The tumor cells were immunoreactive for WT1 antibody. Molecular testing for WT1 mutation by sequencing exons 7 and 9 of the Wilms tumor gene *(WT1)* was carried out using the ABI 3730 XL® automated sequencer. The tumor was positive for the *R462Q* mutation (Figure 2, first panel).

Case 2: A 20-month-old male presented with a large abdominal mass. CT scan revealed a well-defined, 10 cm, partly cystic mass arising in the lower pole of the right kidney and compressing the renal pelvis causing hydronephrosis (Figure 3A). The contralateral kidney appeared normal. The nephrectomy specimen measured 11 x 8.5 x 7 cm and weighed 422 g. The cut section revealed a well circumscribed greyish white 10 cm mass involving the kidney. Part of the mass projected into the renal pelvis in a coarse nodular and papillary pattern (Figure 3B). A 2.4 cm rim of unremarkable renal tissue was noted at the periphery of the mass. On microscopic examination the tumor revealed foci with a triphasic pattern consisting of blastemal, epithelial and mesenchymal components. The tumor projecting into the renal pelvis had a predominant triphasic pattern (Figure 3C). Approximately 90% of the tumor showed rhabdomyomatous elements with occasional foci of smooth muscle differentiation (Figure 3D-E).

(Turk Patoloji Derg 2019, 35:61-68)

Received : 11.01.2016 **Accepted :** 31.05.2016

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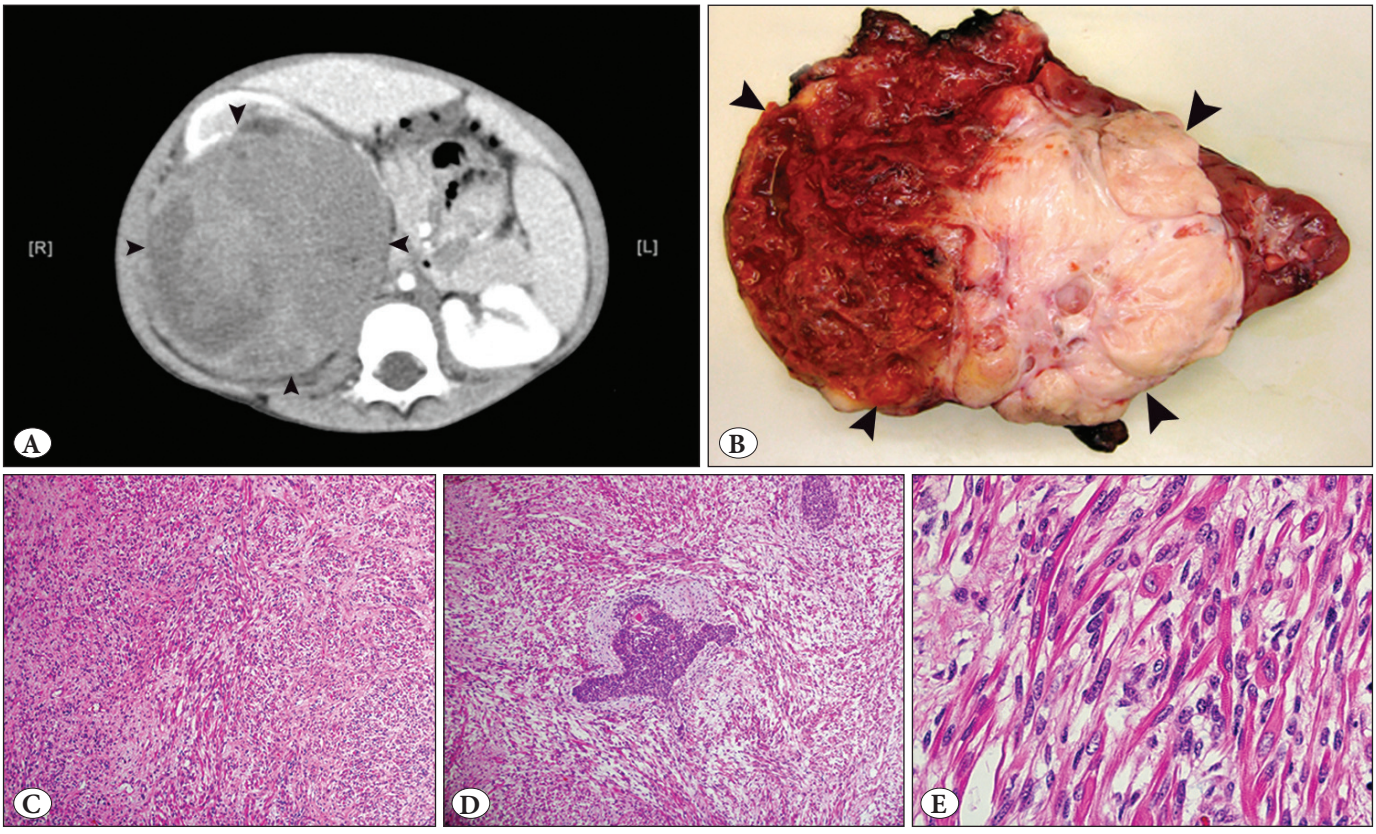

Figure 1: A) CT scan of abdomen revealing a large mass (arrowheads) almost completely replacing the right kidney, **B)** Nephrectomy specimen revealing a large mass replacing the kidney. Part of the mass greyish tan and well preserved while other part is hemorrhagic and partly necrotic (arrowheads). **C)** Neoplasm with diffuse spindle cell proliferation (H&E; x100), **D)** Neoplasm with abundant spindle cell component and undifferentiated epithelial cells (H&E; x100). **E)** Abundant skeletal muscle component of the tumor (H&E; x400).

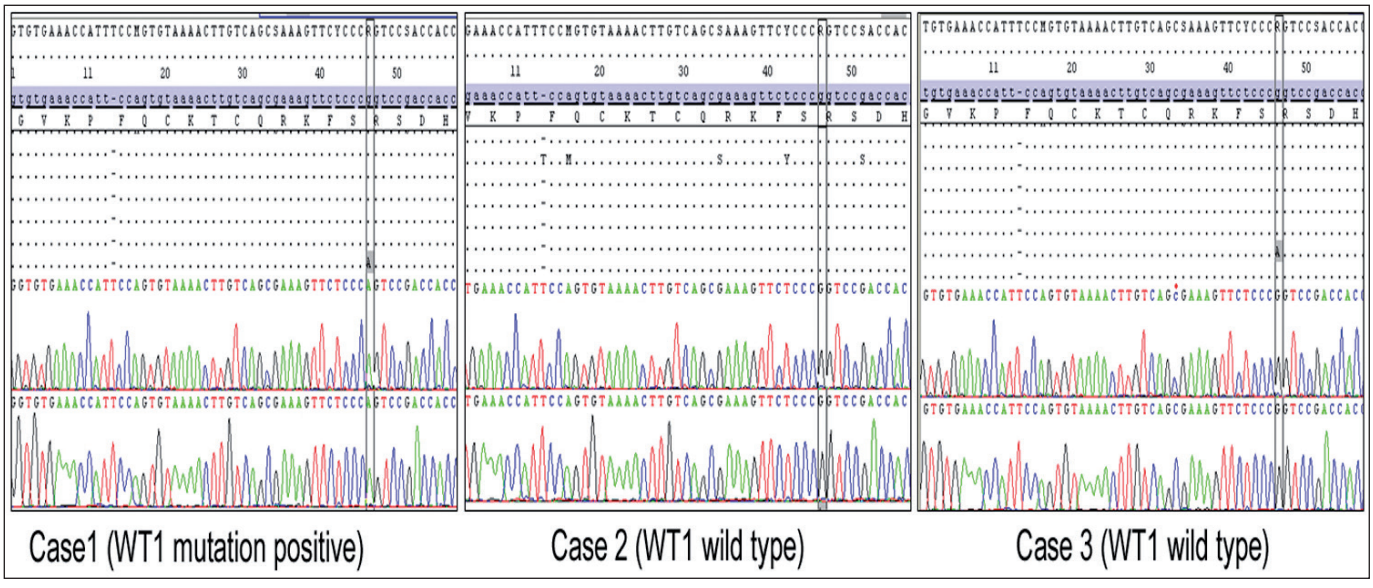

Figure 2: DNA sequence chromatograms in each of the three cases in the study. Analysis of WT1 exon 7 and exon 9 was done by direct sequencing showing one case of WT1 mutation positive (Case 1) and two cases of WTs wild type (Cases 2 and 3). Columns indicate the location of the mutation.

The tumor was limited to the kidney. Surgical resection margins and hilar lymph nodes were free of tumor. There was no anaplasia. The tumor cells were immunoreactive for WT1 antibody. Molecular studies for WT1 mutation by sequencing revealed wild-type *WT1* gene. No mutation was detected (Figure 2).

Case 3: An 11-year-old female presented with an abdominal mass discovered following trauma. CT scan showed an 18.0 cm right renal mass extending from the lower part of the kidney (Figure 4A). The mass compressed the inferior vena cava and renal pelvis causing hydronephrosis. The left kidney, liver, pancreas and bowel loops appeared essentially unremarkable. The nephrectomy specimen measured 22 x 15 x 10 cm and weighed 1242 g. The cut surface revealed a gray white to dark tan mass in the kidney measuring 18 x 13 x 6 cm with extensive necrosis and hemorrhage. Multiple cystic spaces were present in the upper pole. A thin rim of normal renal parenchyma was noted at the periphery in the lower pole (Figure 4B). Histologically most of the tumor consisted of smooth muscle elements and extensive mature epithelial glandular elements with squamous and goblet cell differentiation (Figure 4C-G). Scattered islands of the usual embryonal epithelial, stromal and blastemal elements were identified. There was no anaplasia. No capsular or lymphovascular invasion was noted. One hilar and one paraaortic lymph node revealed foci of metastatic tumor. Immunohistochemical staining for WT1 was positive. Molecular studies for WT1 mutation by gene sequencing revealed wild-type *WT1* gene. No mutation was detected (Figure 2).

DISCUSSION

Teratoid Wilms Tumor (TWT) is a rare variant of WT that was first described by Variend et al. in 1984 (4). Fernandes et al. further defined the TWT as triphasic tumor in which heterologous elements constituted more than 50% of the mass (5). A large variety of heterologous elements including epithelial and mesenchymal tissues may be seen in TWT. The epithelial elements may include squamous epithelium with keratinization and columnar epithelium

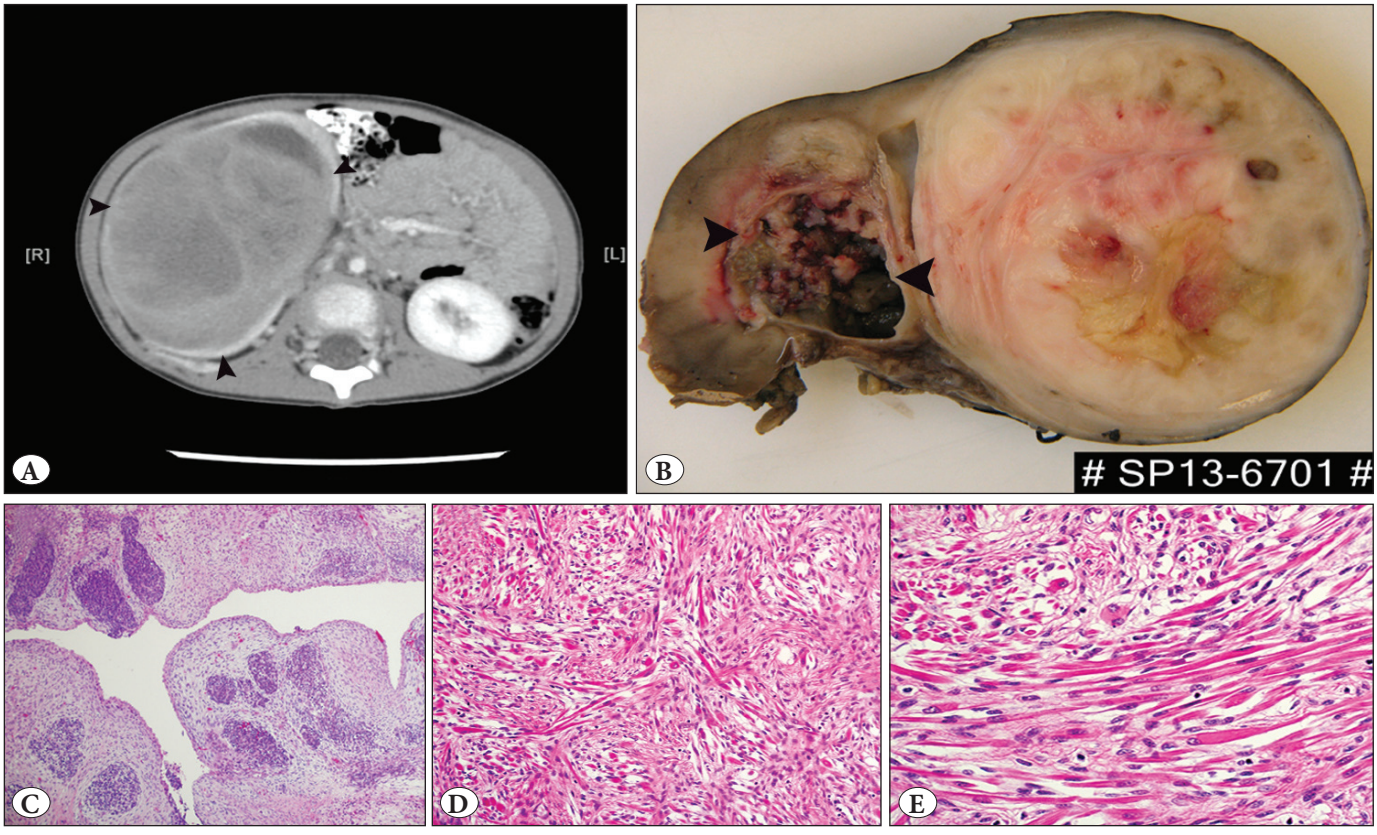

Figure 3: A) CT scan of the abdomen showing a large partly solid partly cystic mass replacing the right kidney. **B)** Cut surface of the kidney revealing a large mass partly replacing the kidney. The cystic area on the left represents dilated renal pelvis with nodular projections of tumor growth (arrowheads) **C)** Triphasic WT projecting into the renal pelvis (H&E; x100), **D)** Dominant tumor component composed of abundant skeletal muscle (H&E; x200), **E)** Higher magnification showing characteristic cross striation within the skeletal muscle tumor component (H&E; x200).

with mucin production, glandular elements of salivary gland, intestine and respiratory tract, and odontogenic epithelium. The mesenchymal heterologous elements may consist of skeletal muscle, smooth muscle, bone, cartilage adipose tissue and differentiated neural tissue.

A review of the literature indicates that till date 30 cases of TWT have been documented (Table I) (4-28). Among the reported cases the age ranged from 3 month to 7 years, which is similar to that seen in the classic WT (1-3). In addition, one case of TWT in an adult patient has been recorded (19).

Extra renal WTs account for around 3% of WTs. Approximately 100 well-documented cases have been reported. These tumors have been encountered in a variety of locations including the retro peritoneum, inguinal and para testicular region, female genital tract, bladder, thorax, and lumbosacral region (2). A review of the literature revealed only five reported cases of extra renal TWT (29-32). The locations of tumors in these reports are sacrococcygeal region, pelvicalyceal junction, vagina and abdomen (Table II).

The reported cases of TWT may be divided into three morphologic categories depending upon the predominant histologic pattern. Some tumors may contain a predominant mesenchymal component such as smooth muscle or rhabdomyomatous elements. These tumors may be categorized as mesenchymal predominant. Some of these tumors have a predominance of well-differentiated rhabdomyomatous component. Such tumors have also been called "fetal rhabdomyomatous nephroblastoma" (33). However, since these tumors seem to fall within the definition of TWT, a separate designation is perhaps unnecessary. The second category includes tumors in which heterologous epithelial components are predominant. Most of these seem to contain abundant squamous epithelium and have been called epithelial or squamous predominant. A third type of TWT may be composed of a heterogeneous

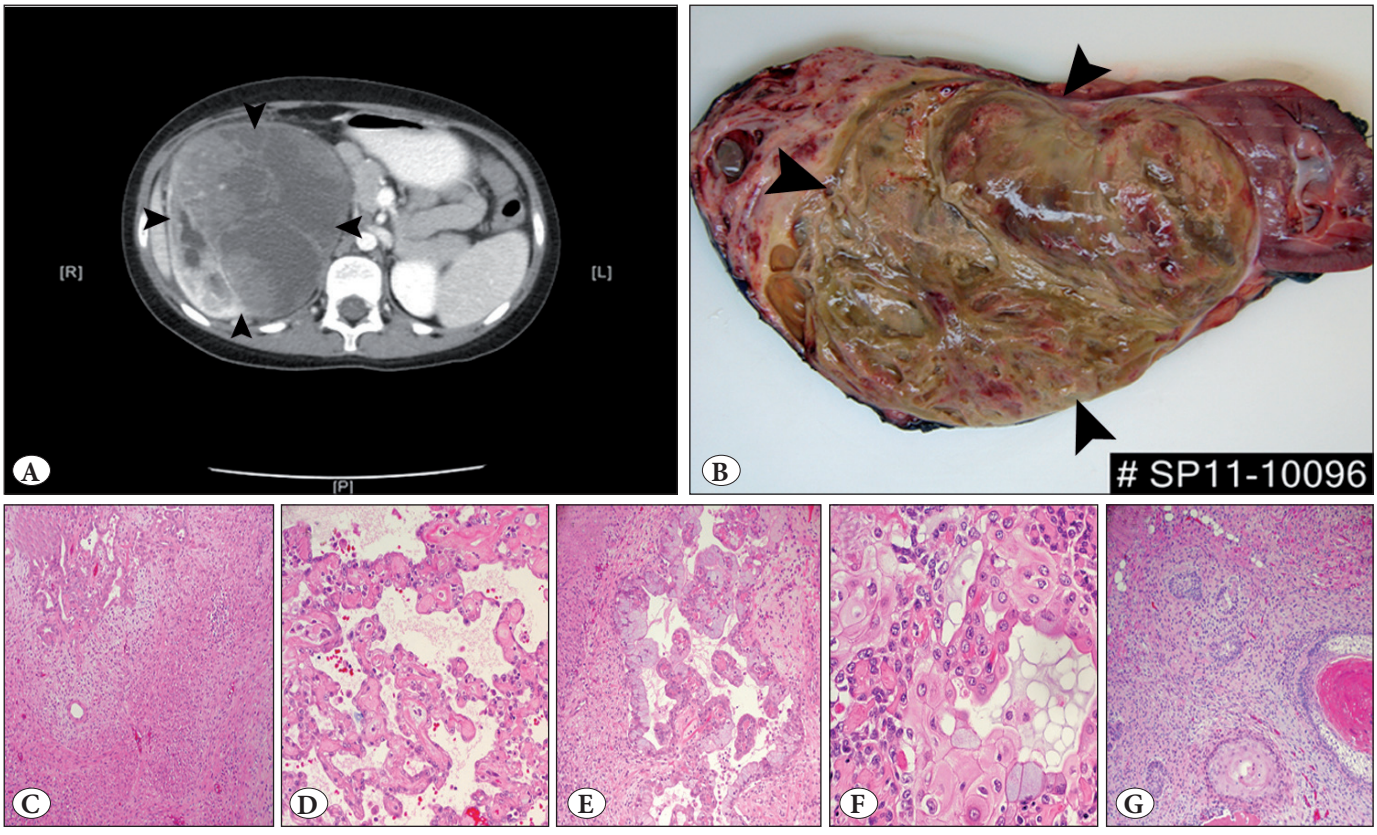

Figure 4: A) CT scan of the abdomen showing a large mass (arrowheads) replacing virtually the entire right kidney. **B)** Cut surface of the nephrectomy specimen revealing a large mostly cystic and necrotic mass (arrowheads) occupying most of the kidney. **C)** Low magnification photomicrograph revealing epithelial and stromal components of the tumor (H&E; x100), **D)** Epithelial tumor component with complex network of cystic spaces line by flattened epithelial cells (H&E; x200), **E)** A representative area within the tumor revealing well-differentiated epithelial cells some showing mucinous features (H&E; x200), **F)** Another area showing well-differentiated mucinous and squamous epithelial cells (H&E; x400),**G)** Mixed epithelial and stromal components including bone and cartilage (H&E; x100).

Table I: Reported cases of Teratoid Wilms Tumor (TWT) in literature

SN.	Author/Year	Age Yrs./Sex	Histology	Follow up*
1	Variend et al. 1984	3/F	Various epithelial and mesenchymal elements.	Unknown
2	Fernandes et al. 1988	2/M	Not reported.	Died, sepsis and renal failure
3	Fernandes et al. 1988	2/M	Not reported.	A&W after 7 years
4	Fernandes et al. 1988	2/M	Not reported.	Post-op course complicated by chronic renal failure
5	Vujanic 1991	1.1/F	Fibro adipose tissue, rhabdomyoblasts, smooth muscle, cartilage, neuroepithelium, squamous, columnar and mucinous epithelium.	A&W after 2 years
6	Magee et al. 1992	2.5/M	Epithelial cells, spindle cells, mature adipose tissue.	A&W after 4 years
7	Magee et al. 1992	0.9/M	Squamous, mucinous columnar epithelium, mature muscle and adipose tissue.	A&W after 1 year
8	Kotiloglu et al. 1994	3/F	Mature adipose tissue, glandular and mucinous epithelium.	A&W after 23 months
9	Williams et al. 1994	3/F	Skeletal muscle, adipose tissue, mucus glands.	Died from extensive pulmonary metastasis
10	Ashworth et al. 1996	3/F	Mucin-secreting epithelium, fibromyxoid stroma, skeletal muscle, cartilage and adipose tissue.	Relapsed at 2 months; unknown outcome
11	Paterson et al. 2000	2/M	Mature adipose tissue, skeletal muscle, connective tissue.	Unknown
12	Karaca et al. 2000	2.5/M	Squamous epithelial component (~70% tumor).	Died; pulmonary relapse at 6 months
13	Bakshi et al. 2003	1.5/M	Predominantly heterologous tissues (adipose, glial, muscle, cartilage, or bone.	A&W after 3 years
14	Cacchetto et al. 2003	4/F	Cylindrical ciliated, cystic squamous epithelium with hair follicles, adipose tissue muscle fibers, rhabdomyoblasts.	A&W after 32 months
15	Inoue M 2006	0.4/M	Stratified squamous, columnar epithelium, pigmented, mature adipose, and cartilage and bone tissue.	A&W after 3 years
16	Myers JB 2007	4.5/F	Keratinized squamous and nodules resembling epidermoid cysts (> 50% of tumor volume).	A&W after 4 years
17	Koksal Y 2007	2.5/M	Mature adipose tissue, skeletal muscle, bone, cartilage and neurons.	A&W 16 months
18	Parikh B et al. 2007	1/M	Heterologous/ blastemal elements.	Not reported
19	Seo J et al. 2008	50/M	Heterologous elements: skeletal muscle, cartilage, adipose Tissue, neural tissue; squamous epithelium.	Not reported
20	Kajbafzadeh A 2009	4/M	Stromal elements, cartilage, calcification, smooth muscle fibers. Few squamoid areas.	A&W 9.5 years
21	Gupta R 2009	4/M	Cystic wall with colon-type muscular wall	A&W 5 months
22	Sultan I 2010	2/M	Skeletal muscles and mature fat (~85% of the tumor)	A&W 20 months
23	Sultan I 2010	5/F	Rhabdomyoblastic, mature adipose tissue, mucin-producing columnar epithelium	Relapse followed by remission; no evidence of disease
24	Sultan I 2010	0.11/F	Skeletal muscles, mature adipose tissue and osteoid. Glandular, squamous epithelial with focal pilosebaceous	A&W 9 months
25	Mukhopadhyay 2011	4/F	Mature mucous epithelium and rhabdomyoblasts.	Unknown
26	Treetipastit 2011	0.9/M	Skeletal muscle, mature adipose tissue, bone, small islands of odontogenic epithelium	Unknown
27	Yadav 2012	2/M	Squamous with keratin pearls (~75%); adipose and glial tissue	Unknown
28	Bardesi 2012	4/M	Cysts lined by flattened, stratified squamous epithelium, keratin flakes. Focal spindle cells /smooth-muscle differentiation	A&W 21 months
29	Sinha A 2013	2/M	Squamous epithelium; abundant keratin pearls (~75%)	A&W 1 year
30	Ramani M 2013	0.3/M	Skeletal muscle; stratified squamous epithelium with keratinization	Unknown
31	Current Case 1 1025	2/M	Rhabdomyomatous differentiation ~90%. Multiple foci of squamous differentiation and mature adipose tissue.	A&W 7 month follow-up
32	Current Case 2 1025	1.8/M	Rhabdomyomatous differentiation ~90%; focal smooth muscle differentiation	No recurrence; last follow up 2 mo post-chemo
33	Current Case 3 1025	0.11/F	Mature epithelium with squamous and goblet cell differentiation. Stroma with smooth muscle differentiation	No recurrence within 2 year follow-up.

A&W: Alive and well.

Table II: Reported cases of extra renal Teratoid Wilms Tumor (TWT)

SN.	Author/Year	Age Yrs./Sex	Location / Histology	Follow-up
1	Pawel 1998	7/M	Partly cystic ureteropelvic mass; extensive squamous and columnar cell elements with areas of classic WT	A&W 18 months
2	Song 2010	13/F	6x5 cm mass in vagina; myxoid spindle cells with rhabdomyomatous differentiation. Variably sized tubular structures lined by pseudostratified columnar or cuboidal cells	A&W 97 months
3	Song 2010	1 day/ F	15 cm multiloculated sacrococcygeal mass; skeletal muscle, bone cartilage, squamous epithelium, ciliated mucinous; blastemal/ nodular blastemal.	No follow up provided
4	Chowhan 2011	1.3/ M	Retroperitoneal mass below the left kidney. Predominantly glandular epithelium with skeletal adipose tissue and glial tissue	A&W 6 months
5.	Baskaran D 2013	3/M	Undifferentiated blastemal, adipose tissue, skeletal Muscle, cartilage, myxoid fibroblasts	A&W 1 year

A&W: Alive and well.

mixture of heterologous epithelial and mesenchymal elements without any of these components becoming predominant. This type of TWT may be categorized as having a mixed pattern.

The most important differential diagnosis for TWT is intra renal teratoma and metastasis from a germ cell tumor arising in another location. Teratoma of the kidney is extremely rare and most have been dismissed as cases of TWT or retroperitoneal teratomas secondarily invading the kidney. The differentiation between these two neoplasms in the kidney is often problematic. Although teratomas and teratoid WT may have similar histology, teratomas display unequivocal organogenesis such as stratified squamous epithelium associated with skin adnexa, intestinal mucosal epithelium surrounded by smooth muscle bundles, and neuroglial tissue associated with choroid plexus epithelium (34). In occasional cases of TWT, the serum AFP levels may be elevated. This finding should not be interpreted as an argument in favor of a renal teratoma (10,18,30). In cases where adipose or smooth muscle elements are predominant, the possibility of angiomyolipoma may also be considered in the differential diagnosis. Angiomyolipoma is composed of mature smooth muscle and adipose tissue. Angiomyolipoma belongs to the perivascular epithelioid cell family of tumors, known to be immunoreactive for smooth muscle and melanocytic markers (35). Furthermore these tumors lack the embryonic cellular elements of blastemal tissue that are usually present in TWT.

Wilms tumors may manifest genetic abnormalities in one of the two regions in the short arm of chromosome 11 namely 11p13 (WT1) and 11p15 (WT2). Cytogenetic studies in nine reported cases of TWT have revealed 11p deletion or monosomy 11(2). The WT1 gene is located on the short arm of chromosome 11 (11p13). It spans approximately 50 kb and includes 10 exons, encoding a 3 kb mRNA. The carboxyl-terminal portion (Exon 7-10) contains 4 zinc finger motifs, which form the DNA-binding domain. WT1 can bind, through its zinc fingers, to the promoter regions of a multitude of putative downstream target genes. All mutations in WT1 alter the structure of the DNA binding domain, which changes its ability to bind to DNA, resulting in loss of function (2).

Park et al. described the CT features of teratoid Wilms: It usually appears as a cystic renal mass with multifocal, solid components containing fatty elements and occasional calcifications. These authors also noted that theses tumors have diverse features, such as bilaterality, a tendency to extend into the collecting system, and association with nephroblastomatosis (36).

Our series of three cases although small equals two other largest series reported till date. The salient features of all the reported cases, including the current series, is briefly presented in Table I. Our cases were relatively younger than most of the reported series. The histological features in our series were more or less comparable to other reported cases; however, all our cases had good outcome, despite one of the cases showing lymph node disease (Case 3). Although germline mutations of *WT1* gene have been detected in children with genetic predisposition to WT mutational analysis of our cases was limited to tumor tissue only. Similar to the reported incidence (~20%) of *WT1* mutations in sporadic WT only one of our three cases showed *WT1* mutation (2). Interestingly, data on *WT1*

gene mutation in TWT is sparse and our study indicates that they are not dissimilar to typical cases of WT with mutation being present in only a small minority.

The treatment of TWT patients has not yet been established because of the entity's rarity and varying tumor components. Surgical resection appears to be the treatment of choice due to relatively inconsistent tumor response to chemotherapy and radiation. Most of the reported cases have been shown to be free of recurrence or metastatic disease following nephrectomy. In two cases, however, pulmonary metastases were reported (Table I). One of our patients also had metastatic tumor to the regional lymph nodes. TWT cases do not usually respond to chemotherapy. Resistance to chemotherapy may be due to the presence of a high proportion of relatively mature heterologous tissues within the tumor. As the neoplastic tissues continue to differentiate, tumors may even increase in size while undergoing therapy, giving the false impression of an aggressive biology.

CONFLICT OF INTEREST

None of the authors involved in this work has any conflicts of interest, financial or otherwise.

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