PATHOLOGICA 2023;115:333-340;
DOI: 10.32074/1591-951X-943

Case Report

A rare case of extrarenal Wilms tumor of the uterine corpus: comprehensive genomic profile and review of the literature

Lara Alessandrini[1], Angela Guerriero[1], Giada Munari[1,2], Biancamaria Del Forno[3], Luisa Santoro[1], Matteo Marchetti[4], Margherita Nardin[5], Roberto Tozzi[4], Matteo Fassan[3], Angelo Paolo Dei Tos[3]

[1] Surgical Pathology Unit, University Hospital of Padova, Padova, Italy; [2] Istituto Oncologico Veneto IRCCS, Padova, Italy; [3] Department of Medicine (DIMED), Surgical Pathology & Cytopathology Unit, University of Padova, Padova, Italy; [4] Department of Women and Children's Health, Gynecology and Obstetrics Unit, University of Padova, Padova, Italy; [5] Radiology Unit, Istituto Oncologico Veneto IRCCS, Padova, Italy

Summary

Wilms tumor (WT), or nephroblastoma, is an uncommon malignant neoplasm occurring in the kidney of pediatric patients. Its extrarenal location is extremely rare and has been reported in various sites, including the female genital tract, with only 9 cases arising in the uterine corpus. We present the case of an adult woman who underwent total abdominal hysterectomy due to a uterine mass causing persistent abdominal pain. The characteristic triphasic morphology (composed of epithelial, stromal, and blastemal elements) supported by a broad immunohistochemical panel, along with the imaging exclusion of a renal neoplasm, was diagnostic of WT of the uterus. For the first time, a comprehensive genomic profiling of a uterine primary WT was also performed by next-generation sequencing, disclosing alterations at the level of copy number variations in the genes ERBB2, FGFR23, FGF6, FGFR2, and RPS6KB1. All previously reported uterine cases were reviewed, with a summary of their main clinicopathologic characteristics, and the main differential diagnoses are presented. Further reports are needed to improve our knowledge about prognostic factors, clinical behavior and molecular alterations that could guide appropriate therapeutic decision making.

Key words: endometrial rare histotypes, extra-renal wilms tumor, molecular pathology

Received: November 5, 2023
Accepted: November 7, 2023

Correspondence
Lara Alessandrini
Surgical Pathology Unit, University Hospital of Padova, Padova, Italy
E-mail: lara.alessandrini@aopd.veneto.it

How to cite this article: Alessandrini L, Guerriero A, Munari G, et al. A rare case of extrarenal Wilms tumor of the uterine corpus: comprehensive genomic profile and review of the literature. Pathologica 2023;115:333-340. https://doi.org/10.32074/1591-951X-943

Introduction

WT (also referred to as nephroblastoma) occurs most commonly in the kidneys of pediatric populations. Extrarenal Wilms tumor (EWT) is a rare lesion, mainly occurring in a variety of sites, including retroperitoneum, inguinal region, spermatic cord, mediastinum, chest wall, lumbosacral region, as well as the female genital tract of young patients [1]. To our knowledge, up to 9 previous EWT arising in the uterine corpus are reported in the literature, the majority being diagnosed in adult patients [2-9] (Tab. I). Histopathology of both WT and of its extrarenal counterparts shows a triphasic differentiation, consisting of blastemal tissue, mesenchyme, and epithelium, with eventual heterologous elements in the form of immature cartilage and rhabdomyoblasts. The epithelium is represented by primitive tubules, rosettes, and numerous embryonic glomeruloid structures. Data regarding prognosis and treatment options are limited due to the rarity of this entity.

In addition to classical genetic changes involving WT1 [10], the IGF2 lo-

Table I. Wilms tumor arising in the uterine corpus previously reported in literature.

Publication (1st Author, year) [ref.]	Age	Symptoms	Extrauterine extension (site)	IHC1 positive stains	IHC negative stains	Molecular analysis	Treatment	Outcome (Follow-up)
Bittencourt, 1981	14	Cramps, vaginal mass	Mesosalpinx, posterior vaginal fornix	NA	NA	NA	TAH/BSO, XRT, chemotherapy	Alive, NED (5.7ys)
Comerci, 1993	22	Menometrorrhagia	No	NA	NA	NA	TAH	Alive, NED (2ys)
Jiskoot, 1999	77	Polypoid mass, vaginal bleeding	Peritoneal washing cytology	Desmin, GFAP	NA	NA	TAH/BSO, XRT	Alive, NED (4mo)
Muc, 2001	42	Vaginal bleeding, necrotic protruding mass	Trasmural uterine extension	NA	NA	NA	TAH/BSO, subtotal resection, XRT	Recurrence at 6mo, DOD 1y after recurrence
McAlpine, 2005	44	Vaginal bleeding	No	NA	ER, PR and CD 10	NA	TAH, BSO, complete surgical staging, CHT	Alive, NED(1y)
LeBlebici, 2009	16	Weight loss, abdominal pain, and vaginal bleeding	Parametrial soft tissues, ligamentum rotundum, sacrouterine ligament	Vimentin (B,S), desmin (S),CK (E)	NA	NA	Inoperable, CHT	Dies of CHT complications (few days, not stated)
Garcia-Galvis, 2009	62	Vaginal bleeding	No	CD56, CD57, CD99, NSE (E,S,B) synaptophysin (B,S), CAM5.2 (E), WT1 (E,S), desmin, myoglobin (S)	NEU-N, GFAP, Chromogranin, CK7, CK20, AFP, A-Actin, TTF-1	NA	TAH/BSO, XRT, CHT	Alive, NED(14 mo)
Cao, 2017	60	Vaginal bleeding	No	WT-1, CK, CD56, Vimentin, P53, CD99, ki67(70%)	ER, PR, CK20, Desmin, NSE, SMA and α-Inhibin	NA	TAH/BSO, CHT	Alive, NED(18 mo)
Pinto, 2018	33	Vaginal bleeding, pelvic pain	No	CK, desmin, SALL4, WT1, PAX8, ki67 (80%)	ER, myogenin, myo-D1, S-100, p16, and CD34	NA	Modified radical hysterectomy, BSO, omentectomy	NA
Present case	59	Abdominal pain		See table2	See table2	CNV in genes *FGFR23, FGF6, FGFR2, RPS6KB1*.	TAH/BSO, omentectomy, appendectomy; CHT	Alive, evidence of disease (6 mo)

NA, not available; BSO, bilateral salpingoophorectomy; DOD, died of disease; IHC, immunohistochemistry; NED, no evidence of disease; TAH, Total abdominal hysterectomy; CK, cytokeratins; ER, estrogen receptor; PR, progesterone receptor; E = epithelium; S0 stroma; B = blastema; CNV = copy number variations; None showed anaplasia.

cus [11], the WNT pathway [12], MYCN and TP53 [13], several additional cancer genes that harbor likely driver mutations in WT have been identified. These genes include epigenetic remodellers (SMARCA4 and ARID1A), microRNA processing genes (miRNAPGs) and the transcription factors SIX1 and SIX2 [12,13]. Identifying actionable mutations has led to potential new targets, with some novel compounds undergoing testing in early phase trials [14].

We report a case of EWT arising in the uterine corpus in a post-menopausal woman, and analyzed the tumor for the first time with next-generation sequencing.

Case presentation

A 59-year-old Caucasian woman accessed the emergency unit for worsening abdominal pain for 2 weeks, where a pelvic mass of unclear significance, likely to pertain to the uterus, was found at ultrasound examination. No gynecological symptoms were reported. The patient had a prior history of a shoulder leiomyosarcoma, treated by local excision and radiotherapy, with subsequent negative follow-up. Pelvic CT revealed a 15 x 13 x 10 cm pelvic mass of possible ovarian origin, with frontward and downward displacement of the urinary bladder (Fig. 1A). Uterine fibromatosis was also described, with uterine morphology distortion that made endometrium not assessable. Urgent surgical treatment was recommended. The surgical specimen from total abdominal hysterectomy with bilateral salpingo-oophorectomy (Fig. 1B) was sent for intraoperative frozen section examination. The uterus weighed 1000g and measured 14 x 11 x 8 cm; cut sections disclosed a solid necrotic tumor with hemorrhagic areas, occupying the entire uterine cavity, with transmural infiltration. Intraoperative diagnosis was initially consistent with malignant mixed mullerian tumor (i.e., carcinosarcoma) and was followed by surgical staging including omentectomy, appendectomy and resection of bladders and pelvic peritoneum.

Microscopic examination showed a triphasic malignant neoplasm composed of epithelial elements, a blastemal component, and spindle (stromal) cells (Fig. 2A), infiltrating the full-thickness of the myometrium up to the serosal surface. The epithelium was characterized by small, compact tubules containing cells with mild cytologic atypia and scattered glomeruloid-like structures (Fig. 2B, C). The blastema cells had basophilic nuclei, dense chromatin and scant cytoplasm, formed closely packed structures blending with the epithelium (Fig. 2B, C). The stromal component consisted of bland, spindle fibroblast-like cells outlining blastema nests. Necrotic areas were diffusely present, as well as foci of heterologous elements, such as cartilage (Fig. 2D) and rhabdomyoblasts. Neither normal residual endometrium nor anaplastic features were evident. Microscopic foci of neoplastic tissue were found in both omentum and peritoneum. This case fulfilled accepted criteria for the pathologic diagnosis of adult EWT, such as age older than 15 years, extrarenal site of primary neoplasm, primitive blastematous spindle or round cell component, presence of abortive or embryonal tubular or glomeruloid structures and no evidence of teratoma or renal cell carcinoma [15,16]. Therefore, the final histopathological diagnosis was primary uterine Wilms tumor.

The Bond Polymer Refine Detection Kit (Leica Biosystems) on BOND-MAX automated IHC stainer (Leica Biosystems) was used for immunohistochemistry. The

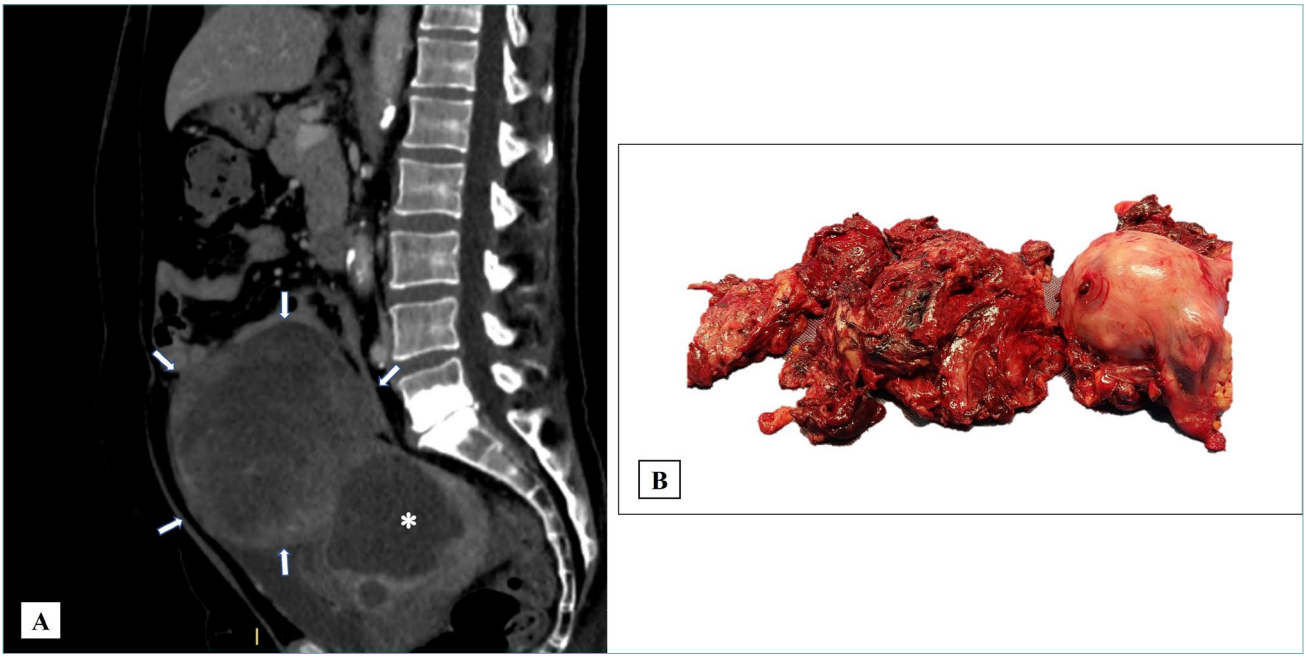

Figure 1. A. Pelvic mass at pre-operative CT scan; white arrows delimits the mass. Necrotic fibroids do not allow clear distinction between the uterus and the mass (*). B. Gross appearance of the uterus enlarged by neoplastic proliferation (right) and frag mented necrotic neoplastic tissue (left).

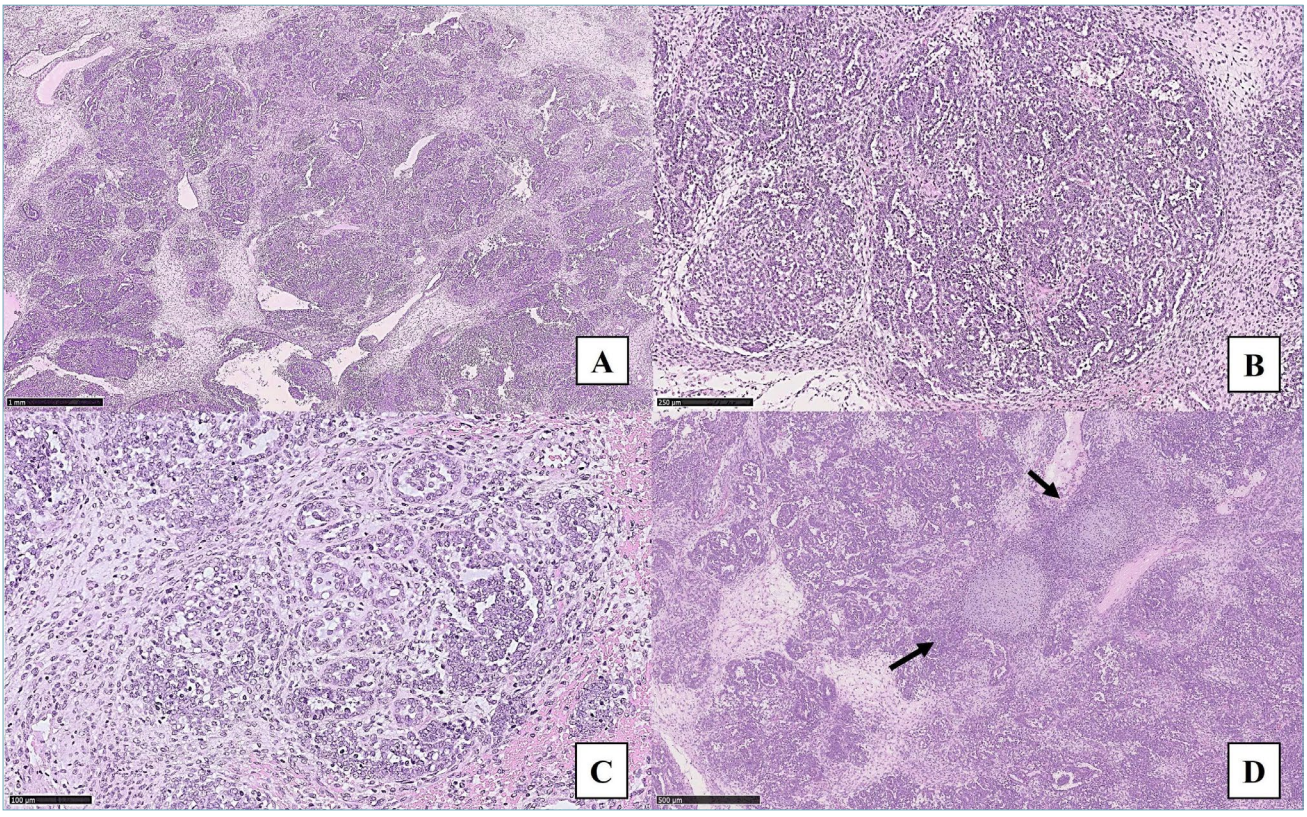

Figure 2. Microscopic panoramic image highlights the triphasic pattern of the neo-plasm composed of epithelial elements, a blastemal component, and spindle (stromal) cells (A). Small tubules and scattered glomeruloid-like structures with mild cytologic atypia,are surrounded by blastema cells with basophilic nuclei, dense chromatin and scant cytoplasm (B,C). The stromal component consisted of bland, spindle fibro-blast-like cells outlining blastema nests (B, C). Foci of heterologous elements, such as cartilage are interspersed (D) (Original magnification 25x, 100x, 200x, 50x, respectively).

Table II. The primary antibodies used, their source and immunohistochemical staining results for each neoplastic tissue component.

Marker	Clone	Dilution	Manufacturer	Expression in neoplastic components		
				Epithelium	Blastema	Stroma
CK AE1/AE3	AE1; AE3	1:100	Novocastra	+	+	-
CK MNF 116	MNF116	1:100	Dako	+	+	-
CK 18	DC-10	Prediluted	Master diagnostica	+	+	-
EMA	E29	Prediluted	Biocare Medical	+	+	-
p53	DO-7	Prediluted	Leica Biosystems	+ (wild type)	+ (wild tipo)	-
PAX8	MRQ-50	Prediluted	Cell Marque	+	+	+
WT-1	BC.6F-H2	Prediluted	Biocare Medical	+ (focal)	-	-
GATA3	L50-823	Prediluted	Cell Marque	+	+	-
Desmin	D33	1:50	Dako	-	+	+
Smooth muscle actin	1A4	Prediluted	Cell Marque	-	-	+
MYF4	LO26	Prediluted	Leica Biosystems	-	-	-
SALL4	6E3	Prediluted	Cell Marque	+	+	-
OCT4	MRQ-10	Prediluted	Cell Marque	-	-	-
CD10	56C6	Prediluted	Dako	+	+	+
CD56	NCAM	1:100	Leica Biosystems	+	+	+
Synaptophysyn	DAK-SYNAP	1:50	Dako	-	+	-
Inhibin	R1	Prediluted	Dako	-	-	-

Table II. *Follows.*

INI1	MRQ-27	Prediluted	Cell Marque	+	+	+
BRG1	3G4	Prediluted	Merck millipore	+	+	+
Calretinin	CAL6	Prediluted	Leica Biosystems	-	-	-
Napsin	RM	Prediluted	Biocare Medical	-	-	-
TTF1	8G7G3/1	Prediluted	Sakura	-	-	-
Estrogen receptor	6F11	1:50	Leica Biosystems	-	-	-
Progesterone receptor	16	1:100	Leica Biosystems	-	-	-
MLH1	ES05	Prediluted	Leica Biosystems	++	++	++
PMS2	EP51	Prediluted	Leica Biosystems	++	++	++
MSH2	79H11	Prediluted	Leica Biosystems	++	++	++
MSH6	EP49	Prediluted	Leica Biosystems	++	++	++
p16	E6H4	Prediluted	Ventana	-	-	-
HER-2	CB11	Prediluted	Leica Biosystems	+(2+)	+(2+)	-
FGFR	D8E4	1:500	Cell Signaling Technology	+	+	-
Ki67	SP6	1:100	Cell Marque	+(60%)	+(70%)	+ (20%)

primary antibodies used, their source and immunohistochemical staining results for each neoplastic tissue component are listed in Table II and highlighted in Figures 3 and 4. In particular, a focal WT1 nuclear faint staining in epithelium with aspecific staining in blastema and mesenchyme, an HER-2 complete membrane

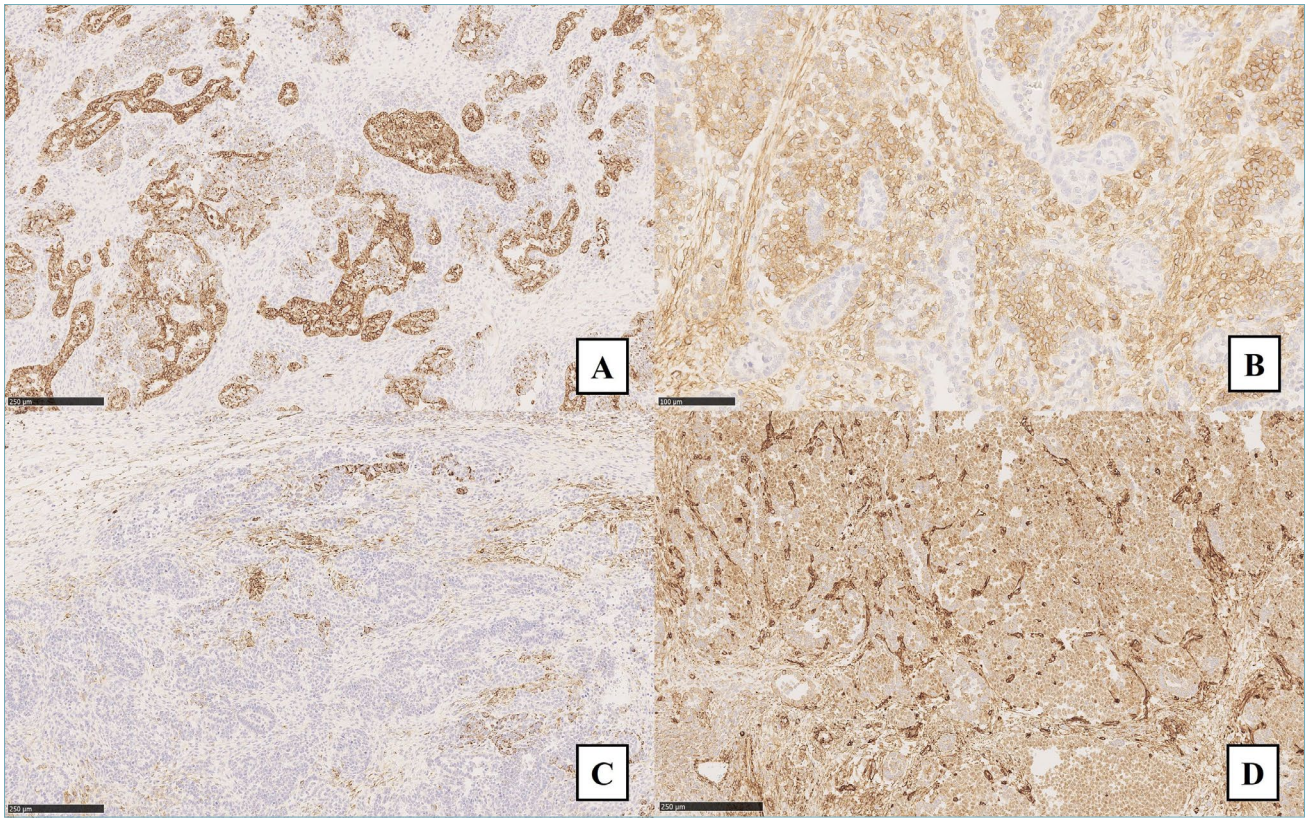

Figure 3. Immunohistochemical positive staining for Cytokeratins (CK AE1-/AE3) in epithelial and blastemal cells is evident in image (A). All three components showed positive staining for CD56 (B).Focal desmin staining was found in both blastemal and stromal cells (C). WT-1 nuclear staining was detected in many epithelial and blastemal cells, with aspecific staining in mesenchymal components (D).(Original magnification 100x, 200x, 100x,100x, respectively).

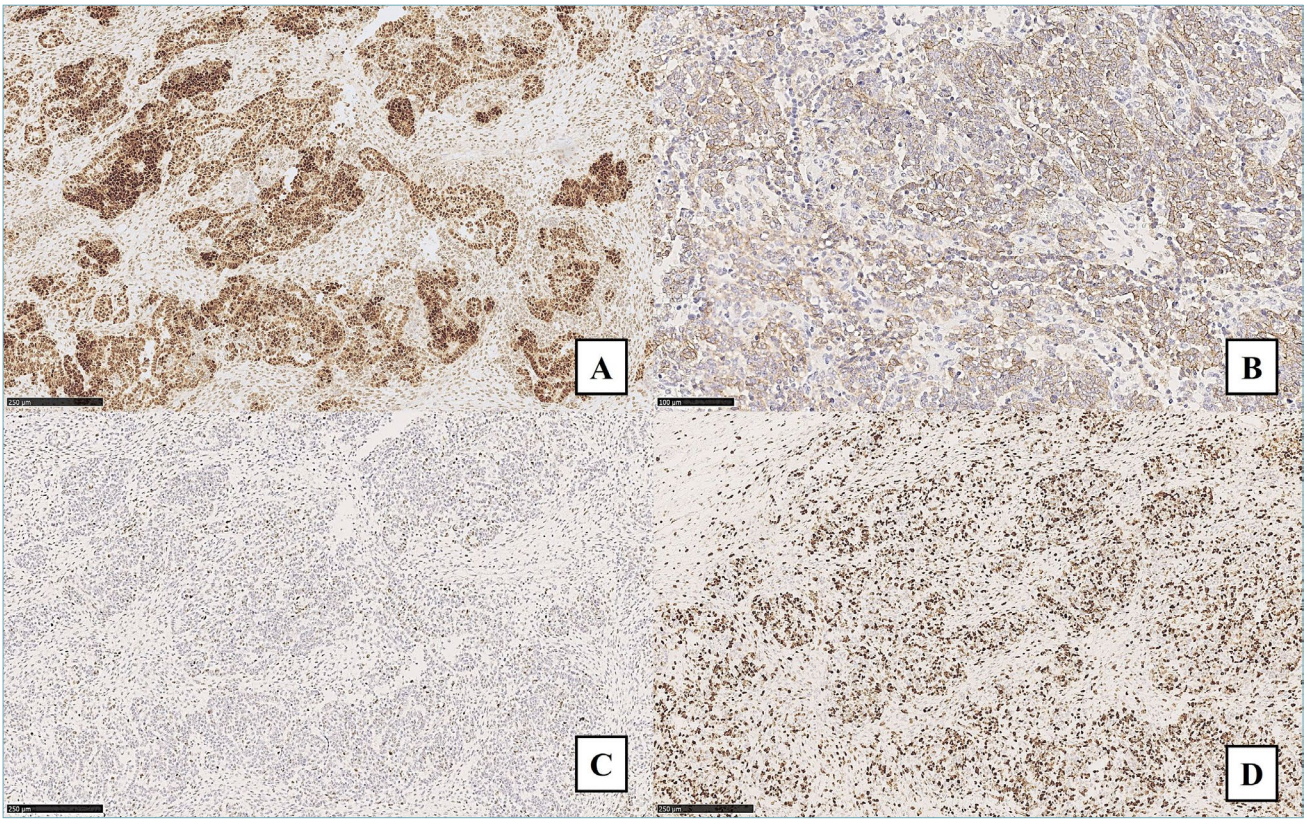

Figure 4. All three components showed positive staining for PAX8 (A). Positive complete membrane HER-2 staining in more than 40% of epithelial and blastemal cells was detected (B).p53 expressed a wild-type pattern (C). Both epithelial and blastemal elements displayed a high Ki-67 index (D).(Original magnification 100x, 200x, 100x,100x, respectively)..

staining with moderate intensity in more than 40% of epithelial and blastemal cells and a pale but diffuse cytoplasmic positivity for FRGF23 in all the three components mirrored molecular findings.

Subsequently, neoplastic tissue was also sequenced using the Illumina TruSight Oncology 500 Assay. DNA and RNA extracted from formalin-fixed paraffin-embedded tissues with the QIAmp FFPE kit (Qiagen) according to the manufacturer's instructions. TSO500 is designed to detect several classes of mutations, including single-nucleotide variants (SNVs), multi-nucleotide variants (< 3 bp), small insertions (1-18 bp)/ deletions (1-27 bp), and is also capable of assessing microsatellite instability (MSI), tumor mutational burden (TMB), fusions and splice variants. The resulting libraries were sequenced on the Illumina NextSeq500 instrument. Libraries were analyzed using the Illumina TSO500 Local App Software v1.3.1 and a customized analysis pipeline within the Clinical Genomics Workspace software platform from PierianDx. Molecular analysis revealed stability at the microsatellite level and unaltered tumor mutational burden (TMB). The alterations revealed by this molecular analysis are at the level of copy number variations in the genes ERBB2, FGFR23, FGF6, FGFR2, and RPS6KB1.

Postoperatively, the patient received 3 cycles of chemotherapy according to the Umbrella protocol, which involves the Carbo-Vp16 scheme (carboplatin and etoposide).

The patient has good performance status, although CT revealed progressive disease at last follow-up (6 months after surgery).

Discussion

The origin of EWT is still debated. Embryologic renal remnants, as metanephric blastema, merged during paramesonephric (Müllerian) ducts may account for the origin of uterine or cervical EWT [2]. Garcìa-Galvis proposed a neometaplasia from a malignant stem cell population differentiating a renal phenotype, as an alternative theory [7].

Their occurrence in an unexpected site and in an un-

usual age group can partly explain the rarity of uterine WTs, as they may not be promptly recognized, possibly being mistaken for various different tumors, such as carcinosarcoma (malignant mixed Müllerian tumor), Ewing sarcoma/peripheral neuroectodermal tumor, endometrioid or serous carcinoma, rhabdomyosarcoma and immature teratoma.

The triphasic morphology, especially the presence of blastema cells around epithelium and low-grade cytology of the stromal and epithelial components are features against the diagnosis of carcinosarcoma, as well as wild-type p53 expression. These aspects were overlooked during frozen section examination and the presence of heterologous cartilage elements, along with a papillary epithelium and an epithelial and stromal high mitotic index, lead to the uncorrect diagnosis of carcinosarcoma. The presence of a tubular-papillary cytokeratin positive epithelium and glomeruloid structures (rather than pseudorosettes) are helpful clues in excluding Ewing sarcoma/peripheral neuroectodermal tumor. Reliance on the sole immunohistochemistry could be misleading in this differential diagnosis, due to the partial overlap of immunophenotype between the two entities [7]. Triphasic pattern, heterologous elements (when present), absence of estrogen/progesterone receptors expression and high mitotic index can rule out an endometrioid carcinoma. Finally, the peculiar triphasic pattern, overall morphology and immunohistochemical findings are supportive of neither rhabdomyosarcoma nor immature teratoma.

Our case shows extrauterine disease and clinical signs of disease progression after adjuvant chemotherapy. On the contrary, favorable outcome was evident in the vast majority of patients, with 7 women out of 10 remaining disease-free between 4 months and 7 years post treatment (Tab. I), whereas only one patient experienced recurrence after 6 months and finally died of disease one year later [5]. Adjuvant radiation and/or chemotherapy were adopted in 8 cases (including ours). However, the number of uterine EWT cases is still too low to draw precise information on their biological behaviour and prognostic parameters that could help in proper stage and guide the choice of the most appropriate treatment. Moreover, the role of well-established prognostic criteria in primary renal WTs, such as presence of anaplasia [17], should be questioned in uterine EWTs, as none of the reported cases showed anaplastic foci. National Wilms' Tumor Study Group (NWTS) protocols are currently applied also to EWTs and are based on the concept of risk-adapted therapy including surgery, chemotherapy and irradiation [18].

The NGS analysis of the genes ERBB2, FGFR23, FGF6, FGFR2, and RPS6KB1 indicated changes at the level of copy number variations.

ERBB2 encodes a member of the epidermal growth factor (EGF) family of receptor tyrosine kinases. ERBB2 enhances kinase-mediated activation of downstream signaling pathways including the MAPK and PI3K pathways. According to a study of 53 female participants, advanced or metastatic endometrial carcinoma with HER2 amplification may benefit from pertuzumab in combination with trastuzumab [19]. Trastuzumab in combination with chemotherapeutic agents is the preferred therapy in HER2-positive advanced (stage III/IV) or recurrent uterine serous carcinoma, according to the NCCN guidelines [20].

Fibroblast growth factor (FGF) ligands and receptors (FGFR) are important components of the cell proliferation and differentiation pathway and are critical in embryonic development, wound healing and angiogenesis [21,22] and their aberrations are frequently found in a wide variety of cancers [22]. Tyrosine kinase inhibitors with targets that include FGFRs have been approved for some tumor types and clinical trials of these agents and other agents targeting FGFRs are ongoing in other solid tumors [23]. RPS6KB1 encodes p70S6K, a protein that phosphorylates multiple substrates involved in protein synthesis regulation. In its phosphorylated form, RPS6KB1 is a marker of mTOR pathway activation, which is implicated in tumorigenesis and is the target of novel specific inhibitors [24].

Conclusions

WT of the uterus is an exceptionally rare malignancy occurring in patients with a broad age range. Proper histopathologic examination associated with a wide immunohistochemical panel are sufficient for a correct diagnosis. Further reports are needed to improve our knowledge about prognostic factors, clinical behavior and molecular alterations that can guide appropriate therapeutic decision making.

Conflicts of interest

The authors declare no conflict of interest.

Funding

This research received no external funding.

Authors' contributions

All listed authors contributed to the production of this manuscript and are listed in the appropriate order. All Authors gave their approval for the publication of the final version of the manuscript. The individual contributions of authors to the manuscript should be specified in this section.

Ethical considerations

None.

References

1 Sastri J, Dedhia R, Laskar S, et al. Extra-Renal Wilms' Tumour--Is It Different? Pediatr Nephrol 2006;21:591-596. https://doi.org/10.1007/s00467-005-0002-5

2 Bittencourt AL, Britto JF, Fonseca LE Jr. Wilms' tumor of the uterus: the first report of the literature. Cancer 1981;47:2496-2499. https://doi.org/10.1002/1097-0142(19810515)47:10<2496::aid-cncr2820471031 > 3.0.co;2-v

3 Comerci JT Jr, Denehy T, Gregori CA, et al. Wilms' tumor of the uterus. A case report. J Reprod Med 1993;38:829-832

4 Jiskoot P, Aertsens W, Degels MA, et al. Extrarenal Wilms' tumor of the uterus. Eur J Gynaecol Oncol 1999;20:195-197

5 Muc RS, Grayson W, Grobbelaar JJ. Adult extrarenal Wilms tumor occurring in the uterus. Arch Pathol Lab Med 2001;125:1081-3. https://doi.org/10.5858/2001-125-1081-AEWTOI

6 Leblebici C, Behzatoğlu K, Yildiz P, et al. Extrarenal Wilms' tumor of the uterus with ovarian dermoid cyst. Eur J Obstet Gynecol Reprod Biol. 2009;144:94-95. https://doi.org/10.1016/j.ejogrb.2008.12.021

7 García-Galvis OF, Stolnicu S, Muñoz E, et al. Adult extrarenal Wilms tumor of the uterus with teratoid features. Hum Pathol 2009;40:418-424. https://doi.org/10.1016/j.humpath.2008.05.020

8 Cao MM, Huang CP, Wang YF, et al. Extrarenal Wilms' Tumor of the Female Genital System: A Case Report and Literature Review. Chin Med Sci J. 2017;32:274-278. https://doi.org/10.24920/J1001-9294.2017.040

9 Pinto A, Huang M, Castillo RP, et al. Wilms Tumor of the Uterus. Int J Gynecol Pathol 2019;38:335-339. https://doi.org/10.1097/PGP.0000000000000500

10 Lee SB, Haber DA. Wilms tumor and the WT1 gene. Exp Cell Res. 2001;264:74-99. https://doi.org/10.1006/excr.2000.5131

11 Maschietto M, Charlton J, Perotti D, et al. The IGF signalling pathway in Wilms tumours--a report from the ENCCA Renal Tumours Biology-driven drug development workshop. Oncotarget 2014;5:8014-26. https://doi.org/10.18632/oncotarget.2485

12 Wegert J, Ishaque N, Vardapour R, et al. Mutations in the SIX1/2 pathway and the DROSHA/DGCR8 miRNA microprocessor complex underlie high-risk blastemal type Wilms tumors. Cancer Cell 2015;27:298-311. https://doi.org/10.1016/j.ccell.2015.01.002

13 Gadd S, Huff V, Walz AL, et al. A Children's Oncology Group and TARGET initiative exploring the genetic landscape of Wilms tumor. Nat Genet. 2017;49:1487-1494. https://doi.org/10.1038/ng.3940

14 Brok J, Pritchard-Jones K, Geller JI, et al. Review of phase I and II trials for Wilms' tumour - Can we optimise the search for novel agents? Eur J Cancer 2017;79:205-213. https://doi.org/10.1016/j.ejca.2017.04.005

15 Beckwith JB, Palmer NF. Histopathology and prognosis of Wilms tumors: results from the First National Wilms' Tumor Study. Cancer 1978;41:1937-48. https://doi.org/10.1002/1097-0142(197805)41:5 < 1937::aid-ncr2820410538 > 3.0.co;2-u

16 Babaian RJ, Skinner DG, Waisman J. Wilms' tumor in the adult patient: diagnosis, management, and review of the world medical literature. Cancer. 1980;45:1713-1719. https://doi.org/10.1002/1097-0142(19800401)45:7 < 1713::aid-cncr2820450732 > 3.0.co;2-u

17 Vujanić GM, Harms D, Sandstedt B, et al. New definitions of focal and diffuse anaplasia in Wilms tumor: the International Society of Paediatric Oncology (SIOP) experience. Med Pediatr Oncol 1999;32:317-23. https://doi.org/10.1002/(sici)1096-911x(199905)32:5 < 317::aid-mpo1 > 3.0.co;2-f

18 Theilen TM, Braun Y, Bochennek K, et al. Multidisciplinary Treatment Strategies for Wilms Tumor: Recent Advances, Technical Innovations and Future Directions. Front Pediatr 2022;10:852185. https://doi.org/10.3389/fped.2022.852185

19 Dumbrava EEI, Balaji K, Raghav K, et al. Targeting *ERBB2* (*HER2*) Amplification Identified by Next-Generation Sequencing in Patients With Advanced or Metastatic Solid Tumors Beyond Conventional Indications. JCO Precis Oncol 2019;3: PO.18.00345. https://doi.org/10.1200/PO.18.00345

20 NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Uterine Neoplasms V.1.2022. Available online: https://www.nccn.org/guidelines/guidelines-detail?category = 1&id = 1473

21 (accessed on 6th February 2023)

22 Brooks AN, Kilgour E, Smith PD. Molecular pathways: fibroblast growth factor signaling: a new therapeutic opportunity in cancer. Clin Cancer Res 2012;18:1855-1862. https://doi.org/10.1158/1078-0432.CCR-11-0699

23 Dienstmann R, Rodon J, Prat A, et al. Genomic aberrations in the FGFR pathway: opportunities for targeted therapies in solid tumors. Ann Oncol 2014;25:552-563. https://doi.org/10.1093/annonc/mdt419

24 Danesh Pazhooh R, Rahnamay Farnood P, Asemi Z, et al. mTOR pathway and DNA damage response: A therapeutic strategy in cancer therapy. DNA Repair (Amst) 2021;104:103142. https://doi.org/10.1016/j.dnarep.2021.103142