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Case Report

Extrarenal Wilms tumor of the recto-vaginal septum with *BRCA2* gene mutation: a case report

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Abstract: Extrarenal Wilms tumor (ERWT) is rare, and its occurrence in the adult recto-vaginal septum is even more uncommon. Importantly, instances of a BRCA2 gene mutation associated with ERWT have not been documented. In this report, we present an unusual case of ERWT situated in the recto-vaginal septum of a 49-year-old woman, accompanied by a concurrent *BRCA2* gene mutation. After the tumor's second recurrence, the patient experienced symptomatic relief after administering poly (ADP-ribose) polymerase (PARP) inhibitor therapy. Given the limited exposure and understanding of optimal treatment strategies for this distinct tumor, there is a definite need to accumulate further clinical experiences and insight. Consequently, we propose that genetic testing be considered in cases involving tumor recurrence or metastasis, since this may offer valuable information for identifying targets for therapeutic intervention.

Keywords: Extrarenal Wilms tumor, recto-vaginal septum, *BRCA2*, poly (ADP-ribose) polymerase inhibitor, case report

Introduction

Wilms' tumor (WT) is the most common malignant kidney tumor in children. While extrarenal Wilms tumor (ERWT) remains rare, cases have been documented mainly in the retroperitoneal and inguinal regions along the spermatic cord, sacrococcygeal region, thorax, chest wall, and uterus [1-3]. ERWT's presence in the adult recto-vaginal septum is even more infrequent. Notably, no instances of a mutation in the *BRCA2* gene associated with ERWT have been recorded. Here, we report the case of an ERWT of the recto-vaginal septum with *a BRCA2* gene mutation in a 49-year-old woman and describe its clinicopathologic features. The patient obtained relief from related symptoms following PARP inhibitor therapy after tumor recurrence. Based on this case assessment, we recommend genetic testing for cases of tumor metastasis or recurrence to identify therapeutic targets specific to the tumor.

Case presentation

A 49-year-old woman was admitted to our hospital due to experiencing abdominal pain and distension persisting for one month. She had previously undergone a total hysterectomy, left salpingectomy, and right salpingo-oophorectomy two years prior as a treatment for uterine leiomyoma. During the physical examination, a discernible mass was palpated between the vaginal wall and the rectum, characterized by a distinct boundary and immobility. Subsequent computed tomography (CT) imaging revealed a solid mass on the right posterior side of the pelvis, which exhibited an irregular shape, measuring approximately 8.9 cm × 6.4 cm × 6.7 cm in dimensions and displayed poor demarcation from the vaginal stump, the posterior wall of the bladder and the adjacent intestinal wall (**Figure 1**). Her levels of preoperative tumor markers were within the normal range. She underwent total tumor resection, left oophorectomy, and omentectomy. Intraoperatively, a distinctive white, firm mass was identified within the recto-vaginal septum, tightly adherent to the surrounding tissues. Scattered tumor nodules with a diameter of 0.2-0.5 cm were observed on the surface of the sigmoid colon, bladder wall, omentum and pelvic peritoneum, while her left ovary was grossly normal. Visually, the tumor measured 10 cm × 8 cm × 8

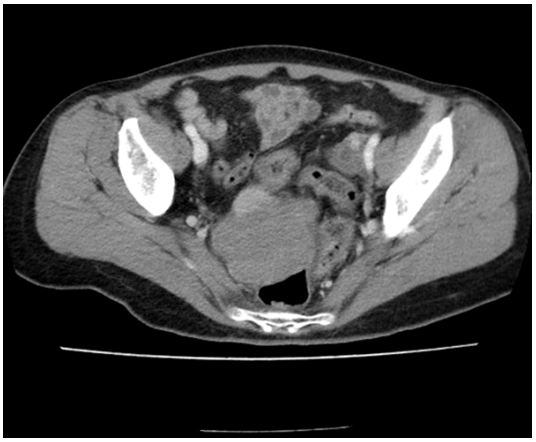

Figure 1. CT scan showing a solid mass on the right posterior side of the pelvis, that is irregular in shape and measures 8.9 cm × 6.4 cm × 6.7 cm.

cm, was rounded, solid with a non-circumscribed border and showed a gray and red fleshy cut surface, accompanied by foci of hemorrhage. Microscopic examination revealed a distinct triphasic pattern within the tumor, comprising epithelial, blastemal, and stromal elements, in addition to abundant admixed heterologous components. The epithelial component was characterized by tubular, reticular, chrysanthemum-like, and glomerular structures (**Figure 2**), distinguished by an abundance of eosinophilic cytoplasm, oval nuclei, and coarse chromatin. These epithelial structures were enveloped by concentric layers of blastemal or mesenchymal cells. The blastemal elements were characterized by small cells bearing hyperchromatic, rounded nuclei and a small amount of basophilic cytoplasm and displayed brisk mitotic activity. They were surrounded by loosely myxoid stroma and arranged in nests or sheets. Spindle-shaped cells formed the predominant mesenchymal component, which intersected between the epithelium and blastemal elements, and a small island of primitive cartilage was also observed. No teratomatous elements were found in the tumor.

Immunohistochemical analysis displayed strong positivity for WT1 and CD56 in both the epithelial and blastemal elements (**Figure 3**), strong positivity for EMA, PCK and PAX8 in the epithelium, strong positivity for vimentin in the stromal elements, and strong positivity for S-100 in the primitive cartilage. However, the tumor tested negative for ER, PR, CA125, P53, CK7, P16, CEA, calretinin, inhibin, Sall4, Cyclin-D1, GATA3, TTF1, CD10, CD99, synaptophysin, chromogranin A, and desmin. The Ki-67 proliferative index was estimated to be around 50%. The final pathologic diagnosis was “extrarenal Wilms tumor of the recto-vaginal septum”. Notably, fluorescence in situ hybridization (FISH) analysis did not reveal any deletions of the *WT1* gene. Postoperatively, the patient underwent adjuvant chemotherapy comprising paclitaxel, ifosfamide, and cisplatin for six cycles with an interval of 4 weeks. Two years after the chemotherapy, CT showed multiple nodules in the pelvis and abdomen. Suspecting possible tumor recurrence or metastasis, two additional rounds of chemotherapy with bevacizumab were administered. However, a second tumor recurrence was observed two years and five months after the second chemotherapy phase. Subsequent tumor tissue next-generation sequencing identified a *BRCA2* gene mutation. The patient was subsequently treated with the PRAP inhibitor therapy Nilapalide, resulting in remission. Impressively, the patient remained recurrence-free during the five-year follow-up after the second chemotherapy treatment.

Discussion

Extrarenal (ER) WT is a rare neoplasm that was first documented by Moyson *et al.* in 1961. It mostly occurs in children and accounts for 3% of all WTs [4]. Although it can manifest in various anatomic locations, the occurrence of ERWT within the recto-vaginal septum has yet to be reported. The affected individuals’ age varies widely, ranging from 1 month to 77 years [5]. Clinical indications of ERWT are non-specific and largely depend on the tumor’s size and location. Therefore, the diagnosis of ERWT is usually made after surgical resection of the tumor and pathologic evaluation of the specimen. Our case occurred in the recto-vaginal septum, and the patient presented with abdominal pain and distension.

The histologic characteristics of ERWT are similar to those of renal WT, including a triphasic mixture of epithelial cells, characterized by a triphasic amalgamation of epithelial cells, primitive blastematous cells, and mesenchymal stroma. ERWT is classified into two categories: pure ERWT and teratoid Wilms’ tumor (TWT), with the latter exhibiting teratoid elements constituting over 50% of the tumor composition. The diagnostic criteria for primary pure ERWT

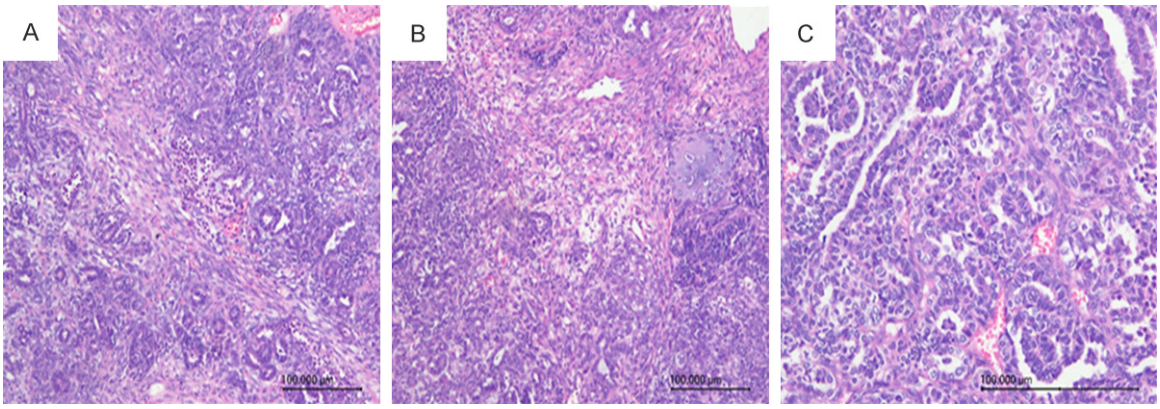

Figure 2. Tumor histopathology. (A) The tumor displayed the typical triphasic pattern of epithelial, blastemal, and stromal elements components (H&E ×100) and (B) a small island of primitive cartilage (H&E ×100). (C) The epithelium showing tubular, reticular, chrysanthemum-like and glomerular structures (H&E ×200).

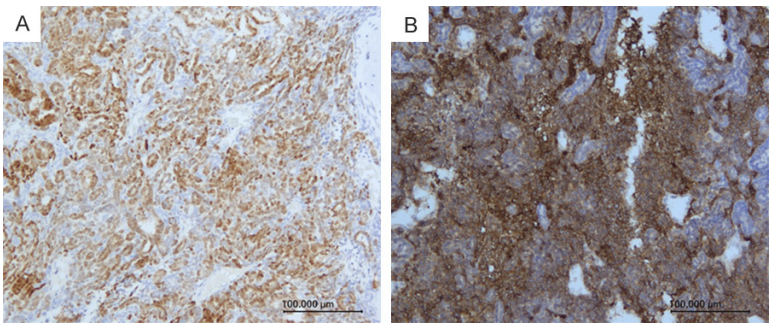

Figure 3. Tumor immunophenotype. (A) Both epithelial and blastemal elements were strongly positive for WT1 (DAB ×100) and (B) strongly positive for CD56 (DAB ×100).

include: (1) occurrence in an extrarenal site; (2) presence of primitive blastemal components; (3) abortive or embryonic tubular or glomeruloid structures; and (4) absence of teratoma or renal WT [6, 7]. In this present case, the tumor was composed of epithelial and metanephric blastema and stromal derivatives at variable stages of differentiation, did not contain teratoma, and fulfilled the diagnostic criteria of ERWT.

The origin of ERWT remains unclear, and multiple perspectives exist regarding tissue origins, such as: (1) tumors in the vagina, uterus, ovary, testis and groin area are hypothesized to have a mesonephric remnants origin; (2) tumors occurring around the retroperitoneal kidney region are believed to originate from ectopic fragments of the retroperitoneal kidney; (3) tumors in the mediastinum and chest wall are thought to stem from anterior kidney fragments; and (4) tumors in other locations are suggested to originate from embryonic stem cells with multipotent differentiation potential [8, 9]. In this reported case, given the tumor's location in the recto-vaginal septum, we speculate that it may have originated from mesonephric remnants.

ERWT displays distinctive features of multidirectional and multipotent differentiation, characterized by a markedly heterogeneous immunohistochemical expression that lacks specific immune markers for precise diagnosis. Both blastematous cells and early differentiated epithelial cells exhibit robust positivity for WT1. Differentiated epithelial cells demonstrate positivity for PCK and EMA, while PAX8 stains positively in blastematous cells and epithelial cells. The distinction of ERWT necessitates differentiation from metastatic WT, carcinosarcoma, moderately to poorly differentiated Sertoli-Leydig cell tumor, and mesonephric adenocarcinoma. Regarding ERWT diagnosis, the initial step involves excluding the possibility of WT metastasis, particularly when renal lesions are absent, as in our case. Carcinosarcoma, characterized by biphasic morphology comprising high-grade malignant epithelial and mesenchymal components, lacks blastemal elements and renal tubules or glomerular-like structures. Epithelial elements within adenosarcomas typically demonstrate ER positivity, while extrarenal Wilms' tumor is marked by ER negativity.

Moderately to poorly differentiated Sertoli-Leydig cell tumors manifest as nests, hollow or solid tubules, cords, or sarcomatoid stroma, primarily composed of Sertoli cells with variable Leydig cell counts, occasionally accompanied by heterologous components. Immunohistochemically, tumor cells exhibit positive staining for inhibin and calretinin, with most cases associated with *DICER1* gene mutations [10]. Mesonephric adenocarcinoma displays diverse architectural patterns, featuring various combinations of tubular, glandular, papillary, retiform, glomeruloid, sex cord-like, and comedonecrosis-like arrangements. Typically, the tissues are positive for GATA3 and TTF1, with mesonephric remnants often detected at the neoplasm's periphery [11].

The etiology of WT remains unclear, with numerous genetic alterations (comprising mutations and overexpression) involving *WT1*, *WT2*, *CTNNB1*, *WTX*, and *TP53* implicated at different stages of WT tumorigenesis [12]. Mutations of the *WT1* gene on chromosome 11p13 are noted in approximately 25% of ERWT cases [2, 13]. Interestingly, our case did not exhibit *WT1* loss as detected by FISH. Instead, next-generation sequencing (NGS) of the tumor tissue disclosed *BRCA2* mutations, an unreported finding in the existing literature. The *BRCA2* gene, part of the breast cancer susceptibility gene (BRCA) family that includes *BRCA1* and *BRCA2*, plays a crucial role as a tumor suppressor gene. The tumor suppressor genes *BRCA1/2* play a critical role in the repair of double-strand DNA breaks through homologous recombination (HR). Mutations in *BRCA1/2* genes that lead to dysfunctional *BRCA1/2* proteins can compromise genome stability and contribute to the development of various types of tumors [14]. Notably, the patient reported in this study had no family history of tumors. A commonly accepted concept suggests that ERWT in the female reproductive system originates from remnants of mesonephric ducts, rooted in their close embryological relationship between the mullerian ducts, which later fuse to form the uterus and the mesonephros. We speculate that this ERWT in the female reproductive system may have originated from mullerian duct remnants, analogous to the pathogenesis of ovarian cancer. Therefore, it is theoretically possible for *BRCA* gene mutations to occur in ERWT of the female reproductive system. However, due to the limited number of cases, further validation of this concept is needed through additional case reports. Considering the detected *BRCA2* gene mutation, PRPB inhibitor therapy was administered after the second recurrence, resulting in a marked alleviation of the patient's condition. This treatment decision was based on our speculation regarding benefits for the patient.

Due to its rarity, there are no established clinical staging or treatment guidelines for ERWT. Some recommendations propose adopting the National Wilms Tumor Study (NWTS) staging criteria as a framework for ERWT staging [15, 16]. Optimal treatment predominantly involves complete tumor excision, with adherence to specific protocols for adjuvant therapy. Although most documented ERWT cases have exhibited complete resection with favorable histopathology and minimal instances of metastasis, adjuvant chemotherapy is generally advised for all ERWT patients. Chemotherapeutic agents that have proven effective in treating renal WT have demonstrated comparable efficacy in managing ERWT cases [2, 17-19]. In patients where complete tumor removal is not feasible, or those with relapse or metastasis, radiotherapy can be considered an option [20, 21]. In the present case report, the patient experienced multiple metastases in the pelvic and abdominal regions, enduring two recurrences following surgery and undergoing two rounds of chemotherapy. In contrast to previous reports, the *BRAC2* mutation was detected during the second recurrence, following which she was successfully treated with a PRAP inhibitor, and no evidence of disease was found after follow-up for 5 years.

Conclusion

ERWT occurring in the recto-vaginal septum is extremely rare. Due to the lack of typical clinical, laboratory,and imaging features, it is difficult to make a definite diagnosis before surgery, which therefore mainly depends on pathologic examination. ERWT with *BRAC2* gene mutation has not been reported previously. The experience based on this patient suggests that complete surgical resection, postoperative chemoradiotherapy, and PRPB inhibitor treatment may significantly improve the prognosis. The integration of genetic testing is crucial for identifyingcandidate therapeutic targets for

rare tumors characterized by recurrence or metastasis.

Disclosure of conflict of interest

None.

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