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Very late recurrence of Wilms' tumor at the uterus and concurrent BRCA2 risk reduction: A case report

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ABSTRACT

This case report describes a young woman who, after a 24-year disease free interval from her advanced childhood Wilms' tumor, developed a large symptomatic pelvic mass contiguous with the uterus. This proved to be a surgically unresectable recurrent Wilms' tumor and she had an excellent response to systemic chemotherapy. A second attempt at hysterectomy proved unsuccessful, however she was able to undergo an ovarian cancer risk-reducing surgery for a pathogenic BRCA2 mutation which was detected during the care of her cancer recurrence.

1. Introduction

Adnexal masses in young women represent a broad spectrum of differential diagnoses. We present a case of a 26-year-old with a distant history of stage IV Wilms' tumor at age 2, who presented with a pelvic mass found on biopsy to represent recurrent Wilms tumor within the uterus.

2. Case description

A 2 year-old female was found to have bilateral renal masses and lung metastases consistent with stage IV Wilms' tumor, and was managed with a combination of neoadjuvant actinomycin and vincristine chemotherapy and subsequent unilateral nephrectomy, contralateral partial nephrectomy and a partial pneumonectomy via the Societe International D'oncologie Pediatrique (SIOP) protocol. She required several regimens including cyclophosphamide, etoposide, carboplatin and fludarabine however by age 3 had a complete response and no residual disease. No radiotherapy was utilized and she had surveillance imaging via CT with her medical oncologist for the subsequent 10 years. Her medical history was complicated by blindness due to aniridia, cognitive delay, and hypertension. She had normal genitalia but had the criteria of WAGR syndrome otherwise, which may contribute to earlier age of Wilms tumor diagnosis and more frequent bilateral disease [1]. The patient herself had not received genetic testing and she had a strong family history of *BRCA2*+ breast cancer in her mother, maternal aunt and maternal grandmother.

At age 26, she was evaluated as an outpatient for urinary retention and dysmenorrhea. On bimanual examination, she had a firm pelvic mass which was broad and immobile, extending to the pelvic side walls bilaterally. Subsequent imaging included contrasted CT of the abdomen and pelvis, as well as pelvic ultrasound (Fig. 1). The CT identified a 10 × 9 × 9cm solid pelvic mass with extrinsic compression of the bladder and sigmoid colon. There was no evidence of lymphadenopathy, extra-pelvic metastatic disease, or ascites. The residual left kidney was normal appearing, as was the contralateral right retroperitoneum. Pelvic ultrasound showed her uterus displaced anteriorly by a retroperitoneal, homogenous solid 10cm pelvic mass without clear visualization of the adnexa. Tumor markers to suggest an alternative ovarian pathology were normal, with carbohydrate antigen 125 (CA125) of 26 units/mL, lactate dehydrogenase (LDH) of 729 units/L, and human chorionic gonadotropin (HCG) < 5 mIU/mL. Consideration was given to preoperative biopsy, however given her symptoms the decision was made to perform pelvic mass resection, presumably via hysterectomy as the mass was in continuity with the uterus on imaging.

The patient was admitted for definitive surgical management with an intent of exploratory laparotomy and excision of her pelvic mass, with intraoperative frozen section to guide possible surgical staging with hysterectomy. The abdomen was opened through a

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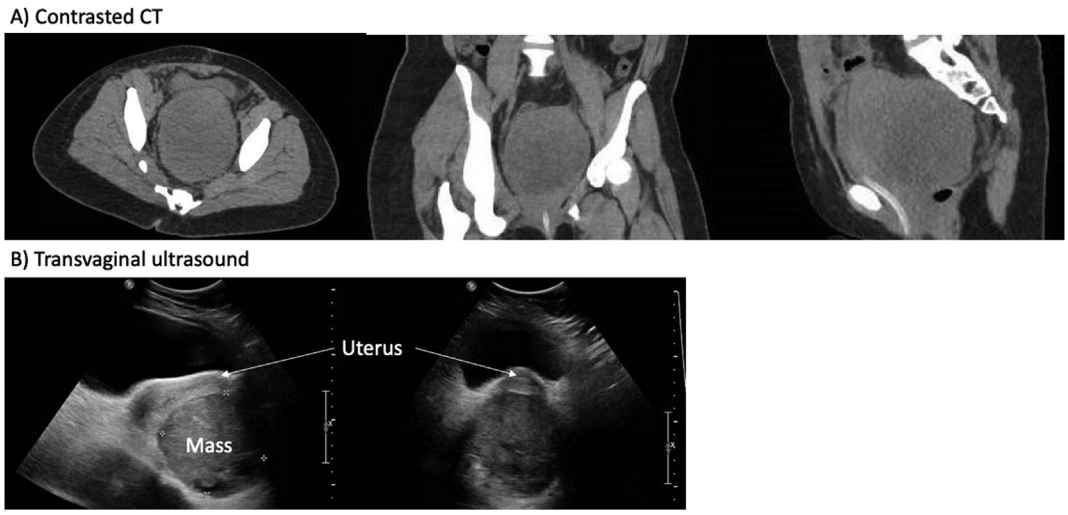

Fig. 1. Pelvic imaging of uterine mass with a) CT and b) transvaginal ultrasound.

midline vertical incision and dense adhesive disease was noted involving the omentum, small bowel and sigmoid colon. Extensive lysis of adhesions was performed to allow evaluation of the pelvis, with findings of a broad pelvic mass indistinguishable from the uterus and extending to the bilateral pelvic sidewalls. The uterine vasculature was not safely accessible due to the immobility of the mass and the tumor was deemed unresectable, thus Tru-Cut core needle biopsies were collected through the superior portion of the mass. The fascia and incision were closed and routine postoperative care was undertaken. Given persistent urinary retention post-operatively, a suprapubic catheter was placed.

Pathology of the core-needle biopsies confirmed that the mass was composed of epithelial tumor cells in tubules with minimal cytoplasm, consistent with epithelial predominant Wilms' tumor recurrence (Fig. 2). Immunohistochemistry confirmed PAX8 positivity, high proliferative index of Ki-67 and was notably negative for ER, PR, and WT1. Given pathology confirmation of recurrent Wilms' tumor, imaging was performed with contrasted CT of the chest to complete her staging assessment, and she was noted to have new development of multiple bilateral pulmonary nodules measuring 8–10mm.

Pediatric and adult medical oncologists were involved to facilitate chemotherapy, and she was started on an alternating regimen of chemotherapy extrapolated from pediatric poor-risk relapse studies [2]. This included ifosfamide 1500mg/m^2, carboplatin AUC4 and etoposide 75mg/m^2 alongside mesna 1500mg/m^2 (ICE) chemotherapy at week 1, 4, 10, 13, 19, and 22 and vincristine 2mg day 1 and day 8 and irinotecan 50mg/m^2 day 1–5 at week 7, 16, 25 and 28. She required dose reductions of the ICE regimen due to neutropenic fever, malnutrition and poor tolerance. Surveillance with postiron emission tomography CT (PET/CT) was performed at intervals throughout her 28 week regimen and showed a significant response with a 95% reduction in the pelvic tumor volume and decreased palpable size of the mass on bimanual examination. She had sub-centimeter lung nodules that were no longer FDG-avid.

Germline genetic testing using saliva was performed confirming a mutation in *BRCA2*. She had a heterozygous mutation at the c.6468_6469delTC locus causing a frameshift mutation. A mutation in *BRCA2* is associated with a 45–84% lifetime risk of breast cancer and 27% lifetime risk of ovarian cancer [3]. Given this finding, the patient and her family were counseled on ovarian cancer risk-reduction strategies in the setting of her recurrent Wilms tumor, particularly as the intent of surgery may be palliative given the short interval of response assessment to chemotherapy. It was discussed that should her Wilms' tumor be unresectable or should her chemotherapy not offer a durable response, that these lifetime breast and ovarian cancer risks were not meaningful and thus, risk reduction interventions futile. Such options could include close surveillance, suppression of ovulation using combined oral birth control pills, completion of bilateral salpingectomy, or bilateral salpingo-oophorectomy. To avoid any future risk or repeat surgical intervention, they elected for definitive bilateral salpingo-oophorectomy. She elected for close screening with examination, MRI and mammography to address her breast cancer risk elevation.

Given her significant response to chemotherapy and *BRCA2* mutation status, she was counseled on repeat attempt at hysterectomy and possible exenteration versus radiation therapy. She was willing to proceed with hysterectomy and bilateral salpingo-oophorectomy but was not agreeable to an extirpative procedure or radiation. Thus, another attempt at surgical management was made via midline laparotomy. Extensive lysis of adhesions was again performed. While the volume of the uterus and mass was smaller than prior, adhesions were too dense to allow a full assessment – the inaccessible nature of the uterine vessels led to the decision that the uterus and mass was unresectable. Given her *BRCA2* mutation, bilateral salpingo-oophorectomy was completed and the surgery was terminated. Pathology of the tubes and ovaries was benign. Routine postoperative care was undertaken and she was able to void spontaneously, allowing removal of the suprapubic catheter.

After 5 months of post-operative surveillance the patient was again counseled on her treatment options including continued surveillance vs radiation therapy vs surgical resection. A repeat PETCT showed non-avid stable lung nodules felt to represent scar, as well as 4 × 3cm pelvic mass confluent with the uterus with minimal avidity at SUV 2.5 (Fig. 3). Given concern for small bowel adhesions and possible involvement at the tumor, the patient was evaluated by the colorectal service who felt that the mass was amendable to complete surgical resection with likely need for bowel resection. She elected for resection. She was taken to the OR and underwent an exploratory laparotomy, pelvic tumor with en bloc hysterectomy and low anterior resection, small bowel resection x2, left ureterolysis and extensive lysis of adhesions. Intra-operative findings were notable for a fixed pelvic mass to the rectovaginal septum, extensive intraabdominal adhesive disease and no evidence of metastatic disease. Final pathology

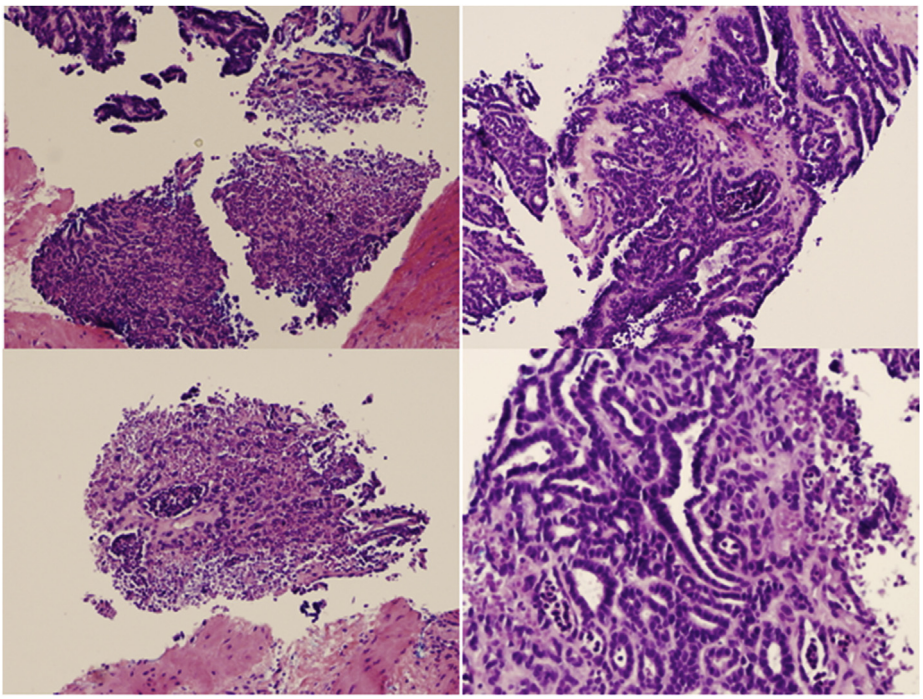

Fig. 2. Histology of the pelvic mass on Tru-cut biopsies.

demonstrated focal (10% of the pelvic mass) viable Wilms' tumor epithelial type without evidence of anaplasia with negative margins. The uterus demonstrated treated Wilms' tumor involving the posterior uterine serosa and myometrium. The patient remains disease free 3 months from definitive surgical management as seen in her post-operative CT (Fig. 4).

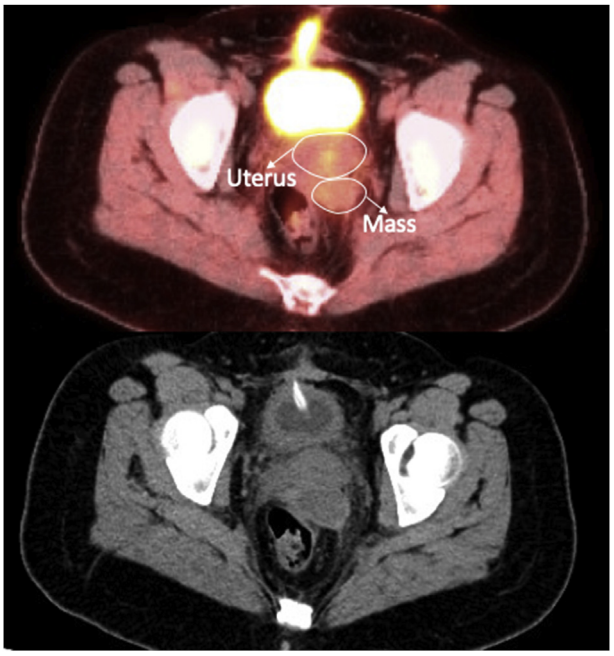

Fig. 3. Post-chemotherapy PETCT assessment of pelvic mass.

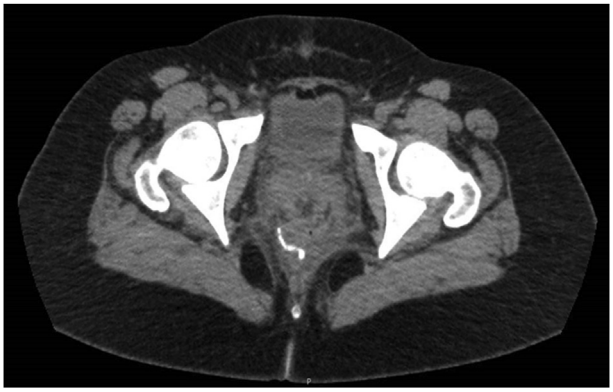

Fig. 4. Post-resection CT

3. Discussion

Wilms tumor is the most common renal tumor in children with an excellent 5-year survival rate of 92% [4]. Extrarenal Wilms' tumors have been reported at the time of initial presentation, including tumors within the uterus and cervix [5–7]. Wilms' tumors recur in 15–20% of patients, with the most common locations of recurrence at the kidney, lung or liver and the mean interval for recurrence at 2 years [4,8,9].

Later recurrences, defined as relapse after 5 years of diagnosis, occurs in 0.5% of patients and clinical outcomes were similar whether recurrence was early or delayed [9]. Very late recurrence at greater than 10 years after diagnosis is rare and has been identified in 10 case reports in the literature (Fig. 5). These have been found in the retroperitoneum, lung, the peritoneum, and in one

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Our Case
Gender	Female	Female	Unknown	Unknown	Male	Female	Male	Female	Male	Male	Female
Relapse time (years)	20	23	10	11	20	13	23	25	18	13	24
Relapse site	Retroperitoneum	Retroperitoneum	Lung	CNS	Lung	Lung	Peritoneum Tumor bed	Pelvis	Lung	Lung	Uterus
References	[9]	[10]	[11]	[11]	[12]	[13]	[14]	[15]	[16]	[17]	

Fig. 5. Case reports of very late Wilms' tumor recurrence [9–17].

case within the pelvic cavity at intervals of 20–25 years from original diagnosis. There are no reported cases of a Wilms' tumor recurrence isolated to the uterus. Senetta et al. hypothesize that initial chemotherapy may ablate the immature elements of a Wilms' tumor, potentially leaving mature, highly differentiated cells unaffected and allowing a long disease-free interval [10].

Survival estimates have improved significantly as chemotherapy, radiotherapy and surgical technique have advanced over the past several decades. While prior to 1984 the 5-year survival estimates were only 20%, advances in treatment have improved the survival estimates for recurrent Wilms' tumor to 63.6% at 5-years for all stages, and specifically 47% at 5-years for high-risk disease [18]. Complete surgical excision may contribute to survival as well [19]. Regimens including ICE or combined vincristine and irinotecan are supported for poor-risk relapsed Wilms' tumor [2,4]. Combined therapeutic approaches with multi-drug cytotoxic chemotherapy, targeted radiotherapy, surgical excision and possible autologous stem cell transplantation are being utilized to good effect [2,20].

This case also highlights the importance of genetic testing. The clinical features of aniridia, blindness and cognitive delay and development of bilateral Wilms' tumors does suggest WAGR syndrome. WAGR syndrome reflects a constitutional deletion on chromosome 11p13 at the *WT1* locus. Only 1% of those affected by Wilms' tumor have an inherited germline mutation, while 10–30% have a new *WT1* or *WT2* germline mutation [1]. It has been proposed that in non-syndromic Wilms' tumor not associated with a *WT1* mutation, that other genes including *REST, CTR9* and *BRCA2* may be associated with familial Wilms' tumor [1].

Biallaelic *BRCA2* mutations are associated with the very rare D1 complementation group of Fanconi Anemia (FAD1) and it is suspected that the *BRCA* and Fanconi Anemia proteins work in linked biological processes resulting in increased risk of breast cancers, medulloblastoma and Wilms' tumors [21,22]. In this FA-D1 group, the probability of developing a Wilms' tumor was 63% by age 6.7 years [23]. There have been case reports of patients with Wilms' tumors and *BRCA2*, specifically one in a family with bi-allelic *BRCA2* mutation causing Wilms' tumor in brothers, with truncating mutations in 886delGT and S1882X [24]. A second report was of a patient with Wilms' tumor noted to have a 6174delT *BRCA2* mutation [25].

4. Conclusion

This case report identifies a unique recurrence in both its timing of 24 years, as well as its location within the uterus. *BRCA2* mutation in Wilms' tumors is rare and this case also addresses the unique role for concurrent ovarian cancer risk-reduction intervention. It highlights the importance of considering recurrent Wilms' tumor in the differential diagnosis for new pelvic masses in women affected by this childhood disease. While pelvic recurrence may lend itself to surgical resection, chemotherapy can be highly effective and should be considered as a neoadjuvant intervention.

Author contribution

All authors contributed to the care of this patient and the preparation of this case report.

Consent

Completed.

Declaration of competing interest

None for any author.

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