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Case report

Management of high-grade ovarian adenocarcinoma in an intraperitoneal pelvic renal transplant recipient

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A B S T R A C T

Background: Number of organ transplant recipients continues to rise worldwide with increasing accessibility and growing advancements in transplant medicine. Transplant patients have at least a two-to-four fold higher risk of developing cancer compared to the general population. As the prevalence of transplant patients increases, a growing number of these patients are expected to present with concurrent conditions such as cancer, requiring more complex and interdisciplinary care.
Case: A 44-year-old patient with an intraperitoneal pelvic renal transplant, found to have high-grade ovarian adenocarcinoma most likely arising from endometriosis, successfully underwent surgical staging, adjuvant chemotherapy, and subsequent pelvic radiation for recurrence. Her kidney function and graft viability were preserved throughout her treatment with careful monitoring.
Conclusion: Management of reproductive tract cancers in kidney transplant recipients is complex. Current practices largely rely on evidence from observational studies and case reports for these cancers and more research is needed in this area.

1. Introduction

Over the past several decades, the number of organ transplant patients have continued to steadily increase with improving success rates driven by the advances in surgical techniques, immunosuppressive therapies, and organ preservation methods (Black, 2018). In 2023, over 46,000 organ transplants were performed in the United States, up from 39,000 in 2020 (UNOS, 2023). Kidney is the most common solid organ transplantation worldwide, followed by liver, heart, and lung (Rosen et al., 2023). As the prevalence of transplant patients increases, a growing number of these patients are expected to present with concurrent conditions such as cancer, requiring more complex care.

Transplant patients have at least a two-to-four fold higher risk of developing cancer and face higher cancer-related morbidity and mortality compared to the general population (Au et al., 2018; Rosales, 2020). Most commonly seen cancers in kidney transplant recipients are thought to be driven by oncogenic viruses as a result of immunosuppression, including Kaposi sarcoma, skin cancer, and HPV-associated anogenital cancers (Au et al., 2018; Rosales, 2020; Tessari, 2013). Therefore, current preventative strategies and treatment approaches throughout the literature largely focus on these subtypes of cancers. Other solid organ cancers such as breast, ovarian, and prostate are more rarely seen in kidney transplant recipients and current practices largely rely on evidence from observational studies and case reports, which are limited (Vernadakis, 2014; Andrikopoulou et al., 2016; Teneriello et al., 1993).

We present here the case of a 44-year-old woman with an intraperitoneal pelvic renal transplant, found to have high-grade ovarian adenocarcinoma, who successfully underwent surgical staging, followed by adjuvant chemotherapy. She had an isolated recurrence in the right pelvic lymph nodes later and subsequently underwent secondary surgical debulking and whole pelvic radiation. We present her case and provide a literature review of the considerations for renal transplant recipients diagnosed with reproductive tract cancers, who inherently carry a higher risk of renal injury and genitourinary compromise in surgical and medical treatments for reproductive tract cancers.

2. Case

44-year-old gravida 0 Caucasian woman with past medical history of polycystic kidney disease, who underwent bilateral nephrectomy and living related intraperitoneal renal transplant at 41 years-old, presented

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with pelvic pain and dysmenorrhea for 6 months. She was maintained on tacrolimus immunosuppressive therapy since her kidney transplantation. Pelvic ultrasound revealed small uterine leiomyomas and complex, but largely benign appearing ovarian cysts in both ovaries, measuring 1.4 cm in the right ovary and 3.4 cm in the left ovary (Fig. 1). Her CA125 was elevated to 40.8 U/mL. CEA and CA19-9 were within normal range. She had a normal serum creatinine (Cr 0.94 mg/dL) and kidney function (eGFR 75 ml/min/1.73 m^2).

She underwent hysteroscopy with dilation and curettage, laparoscopic bilateral ovarian cystectomy and myomectomy by her primary referring gynecologist. Operative findings revealed intraperitoneal right ureter and pelvic kidney transplanted into right external iliac artery and vein (Fig. 2). Bilateral multi-lobulated, complex ovarian cysts were noted, which were thought to be a series of dermoid cysts in the right ovary and a hemorrhagic cyst in the left ovary. Few peritoneal endometriosis implants were noted, but there was no evidence of ascites or peritoneal carcinomatosis on survey of the abdomen and pelvis.

Pathology revealed high-grade adenocarcinoma with clear cell and papillary features. Immunohistochemistry was positive for HNF, napsin, and focally for ER, p53, p16, and WT1. Endometrial curettings revealed detached fragments of high-grade adenocarcinoma with clear cell and papillary features and strips of inactive endometrium with tubal metaplasia. She was referred to Gynecologic Oncology (FR Nezhat) for further management.

She underwent a subsequent positron-emission tomography (PET) scan without intravenous contrast, which revealed a discrete focus of metabolic activity corresponding to the left ovary, presumably malignant in nature. There was also a non-specific and less robust uptake involving the rest of the uterus, and possible metastatic lymph nodes along right internal iliac and lateral pelvic soft tissues associated with the right ovary, which was not able to be adequately characterized due to lack of contrast and mass effect from transplanted right pelvic kidney. There was no definitive imaging findings of suspicious hypermetabolic activity above the level of the aortic bifurcation or chest. She underwent magnetic resonance imaging (MRI) of the pelvis without contrast for better characterization of PET scan findings, which revealed nodules in the right external iliac chain and the common iliac chain with possible metastasis.

She was counseled on the findings and taken back to the operating room for further surgical treatment and staging. She underwent peritoneal washing, total laparoscopic hysterectomy, bilateral salpingo-oophorectomy, omentectomy, right pelvic lymph node dissection and peritoneal biopsies. Dense pelvic adhesions were encountered at time of laparoscopy involving the bladder, anterior cul-de-sac, bilateral ovaries, and the transplanted right pelvic kidney. Anatomy of the presacral space was distorted from prior transplant surgery. Adhesions between the transplanted kidney, uterus and adnexa were carefully lysed to mobilize the transplanted kidney. The native right ureter could be seen retroperitoneally at the pelvic brim and the transplanted right ureter was noted to be intraperitoneal, implanted to the right aspect of the bladder dome, medial to umbilical ligament. Cystoscopy was performed prior to proceeding with further dissection in the pelvic side wall due to the distorted anatomy, which revealed the transplanted ureter at the dome of the bladder. The right pelvic side wall was then meticulously dissected with careful attention paid to the transplanted kidney and ureter.

Two of the right pelvic lymph nodes appeared bulky and were sent for frozen section, which revealed benign lymph nodes. Given that there were no further suspicious pelvic lymph nodes on prior imaging or intraoperatively and considering patient's known diagnosis of high-grade ovarian adenocarcinoma requiring chemotherapy, decision was made to not proceed with further lymphadenectomy.

Final pathology revealed stage 1C2 high grade carcinoma with clear cell features involving both ovaries. Tumor cells were positive for BerEp4 and p53 focally and negative for WT1. Tumor in the left ovary measured 1.6 × 1.5 × 1.5 cm and in the right, measured 0.15 cm. There was no ovarian surface involvement or lymphovascular invasion. Endometrium was unremarkable and negative for metastatic carcinoma. Peritoneal washings, biopsies, omentum and the 2 right pelvic lymph nodes were negative for metastasis.

She was started on carboplatin/paclitaxel adjuvant chemotherapy and monitored with weekly tacrolimus levels with a target of 5 to 8 ng/

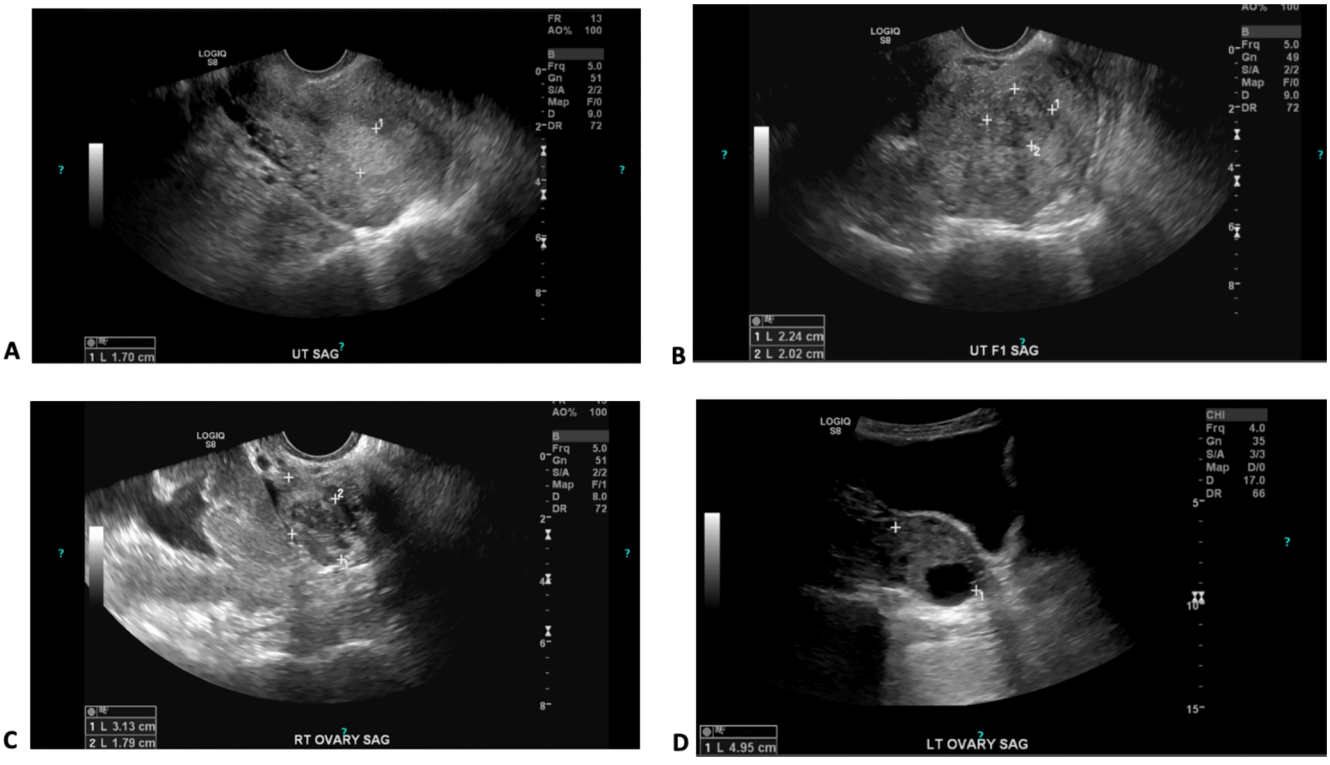

Fig. 1. (A) Laparoscopic view of transplanted intraperitoneal kidney (B) Native right ureter at pelvic brim (arrow).

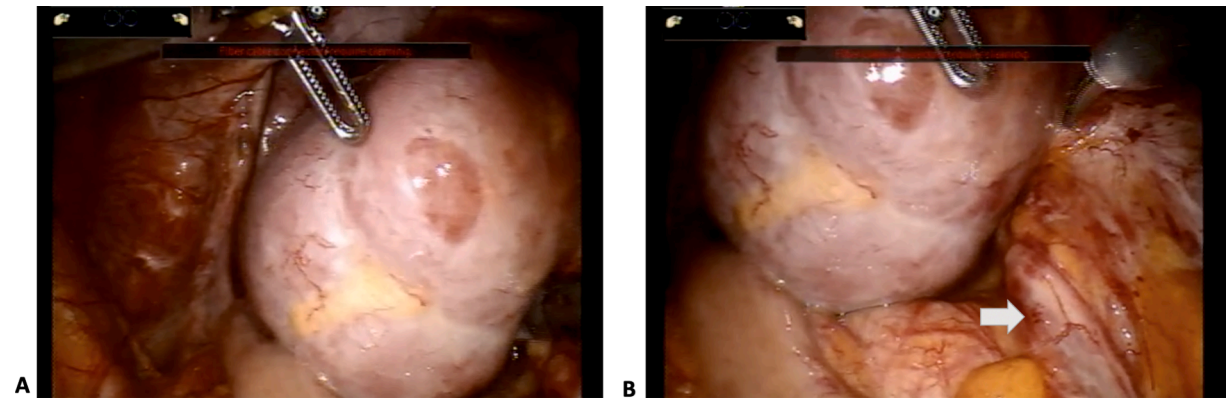

Fig. 2. (A) Retroverted uterus with endometrial echo measuring 1.7 cm. (B) Left lateral intramural leiomyoma (C) 1.4 complex cyst in right ovary, suggestive of a hemorrhagic cyst or endometrioma (D) 3.4 cm lobulated complex cyst in left ovary containing a possible involuting follicle.

mL. Her labs prior to starting chemotherapy were notable only for minimal elevation in calcium up to 11.1 mg/dL, but were otherwise unremarkable with normal creatinine of 0.8 mg/dL and eGFR >60.0 mL/min/1.73 m^2. Further work-up of her elevated calcium revealed parathyroid hormone in low-normal range and negative parathyroid hormone-related protein, normal alkaline phosphatase, thyroid function tests, serum kappa/lambda free light chain ratio, and vitamin D levels.

She completed 6 cycles of paclitaxel at 175 mg/m^2 and carboplatin at AUC of 6 except the last cycle that was reduced to AUC of 5 due to persistent thrombocytopenia. Otherwise, she tolerated chemotherapy well outside of mild lower extremity paresthesia and maintained good renal function throughout her treatment. Her creatinine remained at her baseline range of 0.8–0.9 mg/dL and her calcium normalized without further interventions. Her germline genetic testing was negative for BRCA 1, BRCA 2, and related mutations. Her somatic testing was positive for BRCA 2 mutation.

Surveillance PET scan 10-months after her surgical staging was significant for an enlarged lymph node in the right external iliac chain associated with increasing abnormal hypermetabolism, concerning for nodal metastatic disease (Fig. 3). Previously seen suspicious hypermetabolic activity near the right common iliac nodes were noted to be decreased in size, suggesting positive response to chemotherapy. There was no evidence of local disease recurrence on exam.

After a multidisciplinary discussion including her renal transplant team, she was taken back to the operating room and underwent robot-assisted right pelvic tumor debulking, and left pelvic/para-aortic lymphadenectomy. During secondary surgical procedure, the site of prior dissection had healed well and there was no significant adhesions between the implanted kidney and pelvic side wall. There was no evidence of intraperitoneal metastasis. Retroperitoneal evaluation revealed bulky metastatic lymph nodes in the right obturator fossa, encasing the obturator nerve. No suspicious nodes were identified in the left pelvic lymph nodes or para-aortic lymph nodes.

Right retroperitoneal dissection was started by incising the peritoneum above the pelvic brim to first identify the right external iliac artery and vein in order to protect the transplanted kidney and its vascular anastomoses. Access to the right pelvic lymph nodes was achieved using the retrovessel lateral approach to decrease the risk of injury to renal vessels anastomosed to external iliac artery and vein. These vessels were retracted medially to expose the obturator space. Obturator nerve and hypogastric artery were identified and metastatic right pelvic lymph nodes encasing the obturator nerve were removed safely. Since the implanted ureter was intraperitoneal and medial to umbilical ligament, it was readily identified and protected.

A total of 26 lymph nodes were identified in the final pathology and revealed metastatic high-grade carcinoma in two of five lymph nodes from the right pelvic lymphadenectomy and no evidence of metastatic disease in the remainder of the pelvic and para-aortic lymph nodes. Pelvic washings were negative for malignant cells.

Patient was again discussed in multidisciplinary tumor board and recommended pelvic radiation given the pathology of high-grade carcinoma with clear cell features and lack of response to chemotherapy. She was treated with acetylcysteine and intravenous hydration pre- and post-CT stimulation. She received 6000 cGy of radiation dose to right

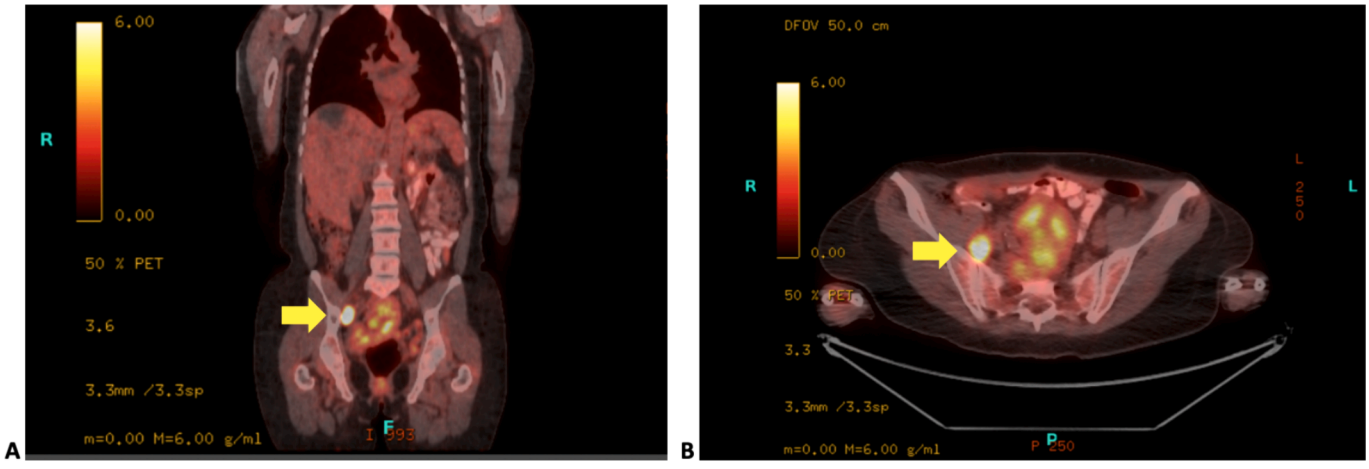

Fig. 3. PET CT images of coronal (A) and sagittal (B) views showing an enlarged lymph node in the right external iliac chain associated with increased hypermetabolic activity, concerning for nodal metastatic disease.

external iliac bed in 30 fractions over the course of seven weeks. During the course of her treatment, she experienced grade I fatigue. Her creatinine was monitored weekly with a slight elevation to 1.02–1.04 mg/dL. Her creatinine has remained stable in this range following her radiation therapy. On surveillance, she has remained disease free clinically and on subsequent PET scans. Her CA125 has remained within normal range over the 8 years since her secondary debulking surgery.

3. Discussion

Transplant patients are a special patient population, who require lifelong close monitoring aimed to prevent graft complications and optimize the long-term success of the organ transplant. General surveillance of kidney transplant recipients includes regular clinical and laboratory evaluation of kidney function, immunosuppressive levels, drug interactions, infections, and malignancies related to long-term immunosuppression (Dantal and Pohanka, 2007).

The increased risk of cancer in kidney transplant recipients is well established with an at least two-to-four fold higher incidence compared to the general population (Au et al., 2018; Rosales, 2020; Tessari, 2013; Vajdic, 2006; Voora and Adey, 2019). While most cancers reported in kidney transplant patients are thought to be driven by suppressed immunity to oncogenic viruses, a growing number of patients are expected to present with solid organ cancers as the prevalence of transplant patients grows.

Surgical and medical treatment options for reproductive tract cancers in kidney transplant recipients are highly complex due to the intricate anatomic relationship of the genitourinary system with the reproductive tract and the toxicities associated with adjuvant treatments. Other factors such as location of the transplanted kidney, previous surgical history with resulting adhesive disease as well as other processes that distort pelvic anatomy such as endometriosis may further complicate surgical interventions. In our case, ovarian cancer is thought to be possibly arising from endometriosis, which has added to the complexity of our case (Nezhat et al., 2015; Nezhat et al., 2002).

The specific location for transplantation of the procured kidney may vary slightly among surgical techniques and individual cases, but the transplanted kidney is generally placed extraperitoneal in the iliac fossa, anastomosing the renal vessels to the external iliac vessels and the ureter to the bladder. The right iliac fossa is generally preferred due to better exposure of iliac vessels on this side compared to the left side obscured by the descending colon. Intraperitoneal placement is often preferred in pediatric patients due to patient size and anatomy limitations. The final location of the transplanted kidney is an important consideration when it comes to surgical staging procedures for reproductive tract cancers, which involve working around the transplanted kidney and ureter for pelvic lymphadenectomy and bladder dissection during hysterectomy. A thorough knowledge of pelvic anatomy and expert surgical skill are essential in navigating the variations from normal anatomy.

Pre-operative imaging studies such as ultrasound, computed tomography, and MRI can help plan for the anticipated pathology and variation in anatomy, however intravenous contrast agents require caution in kidney transplant recipients as both iodinated and gadolinium contrast agents are excreted renally and may affect renal function. Use of acetylcysteine has been shown to reduce contrast-induced nephropathy in high-risk patients and can be administered prior to intravenous contrast administration to limit contrast toxicity (Wu, 2013). Immunosuppressive drug levels and kidney function need to be monitored closely in the peri-operative period to prevent complications of graft injury or rejection. An increase of 20 % to 25 % in serum creatinine above baseline generally warrants attention and further evaluation (Dantal and Pohanka, 2007).

Another important consideration in the management of ovarian cancer diagnosed in kidney transplant recipients is adjuvant therapies, which may include chemotherapy and radiation treatments. Chemotherapy considerations in kidney transplant patients are multifaceted and require the collaboration of a multidisciplinary team. Carboplatin and paclitaxel are commonly used adjuvant chemotherapy agents in ovarian cancer and their dosing and duration require careful consideration due to potential nephrotoxicity and drug-drug interactions with immunosuppressives. Carboplatin, in particular, is renally excreted and requires close monitoring. General consensus throughout literature is also to reduce immunosuppression dose, owing to the fact that immunosuppression may promote cancer growth (Au et al., 2018). This, however mostly applies to cancers with presumed opportunistic viral etiology in immunosuppressed individuals. Ovarian cancer is not considered to fall into this category and currently, there is no quality evidence to suggest reducing immunosuppression dose is beneficial in the treatment of ovarian cancer diagnosed in kidney transplant recipients (Au et al., 2018).

Effect of pelvic radiation therapy in kidney transplant recipients is not well established. Benefits should be weighed against risks case by case. In a case series of six kidney transplant patients with prostate cancer, prostate irradiation showed good tolerance with no kidney injury (Detti, 2022). There are no specific studies that have looked at the effects of pelvic radiation in kidney transplant recipients with ovarian cancer to our knowledge, but in our case report, there was a slight elevation in serum creatinine to 1.02–1.04 mg/dL from baseline of 0.8–0.9 mg/dL after pelvic radiation, which has remained stable in this range post-radiation.

4. Conclusion

Management of reproductive tract cancers in kidney transplant recipients is highly complex owing to the close anatomic relationship of the genitourinary system with the reproductive tract and the nephrotoxicity associated with adjuvant treatments. It is essential that these patients are managed by a multidisciplinary team to prevent complications of graft injury while optimizing cancer outcomes. It is well established that transplant patients carry a significantly higher risk of developing cancer. Current literature largely focuses on preventative strategies and treatment options for cancers deriving from opportunistic oncogenic viruses, which are more common in the transplant patient population. Solid pelvic organ cancers such as ovarian and prostate are more rarely seen, but their prevalence in transplant patients is expected to increase with the growing number of organ transplants worldwide. Current practices largely rely on evidence from observational studies and case reports for these cancers and more research is needed in this area.

Author contributions

ED performed literature review, gathered relevant patient records, and wrote the case report. SC is the prescriber of patient's chemotherapy treatment, who contributed the clinically relevant details of patient's chemotherapy course. RDE is the prescriber of patient's radiation therapy, who contributed the clinically relevant details of patient's radiation therapy course. FRN is the primary surgeon, who performed the patient's initial staging and subsequent secondary debulking surgeries with surveillance follow-up and supervised the preparation of the case report. All authors reviewed the final case report for accuracy and intellectual content and approved the final version for publication.

CRediT authorship contribution statement

Esra Demirel: Writing – original draft, Visualization. **Seth Cohen:** Writing – review & editing. **Ronald D. Ennis:** Writing – review & editing. **Farr R. Nezhat:** Writing – review & editing, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

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