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CASE REPORT

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Modified combined radiotherapy for cervical cancer in kidney transplant recipient

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Abstract

The management of locally advanced cervical cancer in patients with a pelvic kidney transplant is challenging because standard chemoradiotherapy may increase the risk of ureteral stenosis and obstruction or vascular damage of the graft. In the absence of clear guidelines, these patients should be treated using high-precision modern radiotherapy technique.

KEYWORDS

HPV-related cancer, immunocompromised women, locally advanced cervical cancer, modern radiotherapy technique, pelvic kidney graft

1 | INTRODUCTION

This report describes a rare occurrence of locally advanced cervical cancer in a patient with a kidney transplanted in a pelvic position. The patient was successfully treated via modified pelvic radiation therapy so as to avoid irradiation of the transplanted kidney, minimize side effects, yet form an adequate target volume for effective treatment.

According to the current guidelines, concomitant chemoradiotherapy is a standard treatment for locally advanced cervical cancer, including IB2-IV stages of the disease (the International Federation of Gynecology and Obstetrics [FIGO] classification, 2009).[1,2] However, the presence of a pelvic kidney transplant complicates the situation as the altered anatomy must be carefully considered in radiological planning.[3-6] When implanted in the iliac position, the kidney graft is situated in close proximity to the lymph node clinical target volume (CTV) if treated with external beam radiotherapy (EBRT). Furthermore, being close enough to the cervix, the kidney transplant may be affected by significant doses of radiation delivered with brachytherapy (Figure 1). In addition, graft tolerance to radiotherapy and its potential variability between cases are unknown. Finally, concomitant chemotherapy can aggravate immunosuppression, and weekly cisplatin, which is the most widely used regimen, is nephrotoxic.

Management of locally advanced cervical cancer patients with a pelvic transplanted kidney is challenging and requires a modified radiologic approach to find an optimal balance between tumor control and treatment toxicity. With modern radiotherapy techniques, toxicity to the graft can be minimized without compromising oncology outcomes, although evidence for this in the literature includes a limited number of studies.[3-6]

2 | CASE PRESENTATION

The case subject was a 41-year-old woman, gravida two para one, using neither alcohol or tobacco. She suffered from

chronic pyelonephritis in childhood resulted in late-stage renal disease and kidney failure, requiring a kidney transplant. Nine years prior to this study, she had received a donor kidney from her mother. Her renal graft was placed in the extraperitoneal left iliac fossa. Following transplant surgery, she has been receiving immunosuppressive therapy with a calcineurin inhibitor (cyclosporine), a protease inhibitor (everolimus), and a corticosteroid (Medrol).

For 2 months prior to her routine nephrologist appointment, she experienced vaginal bleeding. Her HPV test was positive for type 31 in a clinically significant concentration (6.66 Lg). Morphologic analysis of a cervical biopsy revealed moderately differentiated squamous cell carcinoma.

She was referred to the NN Alexandrov National Cancer Centre for further evaluation and treatment.

On examination, she was normotensive with a blood pressure of 135/90 mm Hg and heart rate of 76 bpm. General examination was unremarkable.

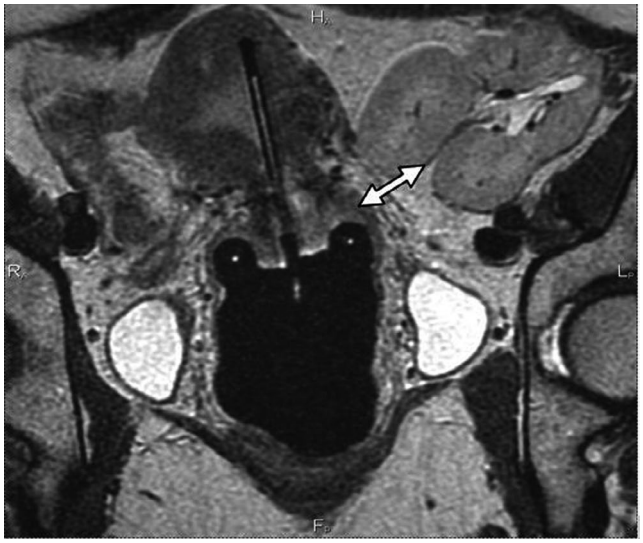

FIGURE 1 The T2-weighted MRI of the brachytherapy applicator in situ, frontal slice, illustrating the proximity of the graft to the uterus (arrow)

2.1 | Investigations

Patient underwent an extensive workup including blood tests, chest X-ray, abdominal ultrasound, gynecological examination, cervical biopsy, and a pelvic magnetic resonance imaging (MRI). Positron emission tomography/computed tomography (PET/CT) was not available at that time in Belarus.

Blood test showed elevated urea (10.0 mmol/L, reference range: 2.5-7.1), elevated creatinine (136.0 micromole/L, reference range: 44-80), and elevated K+ (5.9 mmol/L, reference range: 3.5-5.1). All other blood biochemical parameters were within normal limits.

Her chest X-ray was normal, and her abdominal ultrasound revealed contraction of both kidneys with no paraaortic lymphadenopathy.

Pathology of her cervical biopsy showed fragments of squamous cell carcinoma, grade 2 (Figure 2). The largest fragment was 5 mm, with no clear signs of lymphovascular space invasion. An additional endometrial biopsy showed late-secretory type endometrium.

Pelvic examination revealed normal external genitalia, and speculum examination showed gross tumor of the cervix approximately 4 cm in diameter with extension into the left fornix of the vagina (Figure 3). The rectovaginal examination confirmed a barrel-shaped cervix extending into the left fornix of the vagina. The right parametrium was clear, and the left parametrium had limited access due to the presence of a transplanted kidney.

Magnetic resonance imaging scans in the anterior lip and left part of the cervix identified a tumor, $3.9 \times 2.7 \times 1.5$ cm in size, with infiltration of the anterior and left fornixes of the vagina. There was also invasion of the left parametrium with limited diffusion (functional MRI with diffusion-weighted images [DWI]). There was no extension to the bladder and rectum. Ovaries contained only bilateral follicles. No pelvic lymphadenopathy was noted (Figure 4).

According to the FIGO classification, the patient was diagnosed with stage IIB invasive squamous cell carcinoma of the cervix.

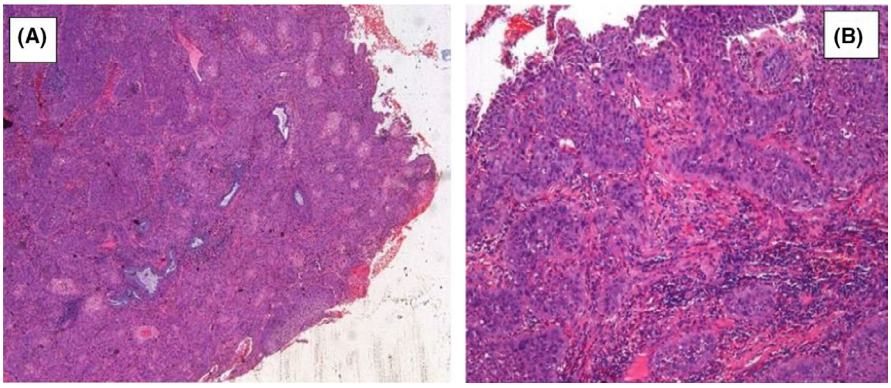

FIGURE 2 Cervical squamous cell carcinoma, grade 2, low power (×2.5) with normal cervical gland remnants (A), and high power (×10) (B)

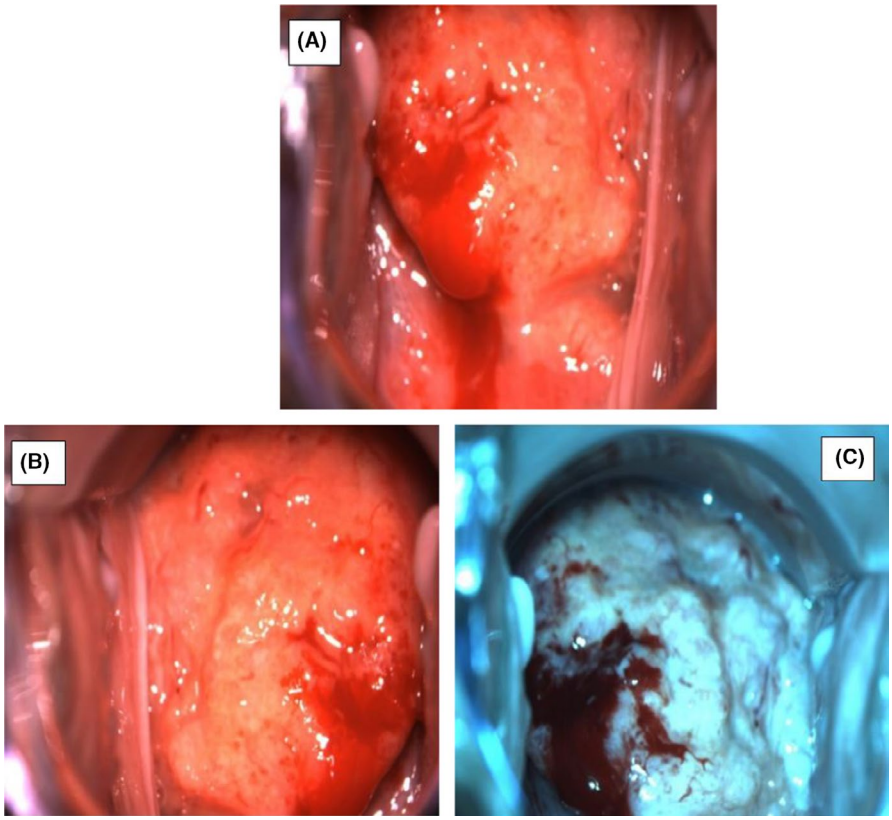

FIGURE 3 Gross tumor mass on the left part of the cervix on speculum examination (A), colposcopy picture after acidic acid application: exophytic lesion and atypical vessels are visible (B), and the green filter enhances visualization of atypical blood vessels (C)

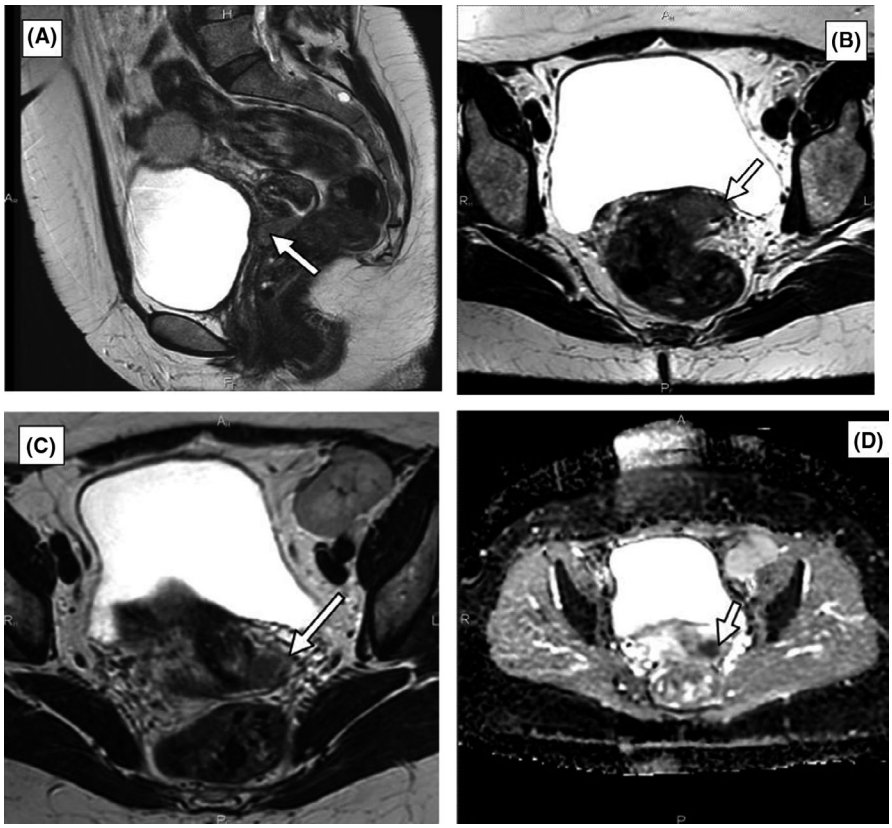

FIGURE 4 Tumor visualization with sagittal (A) and axial (B) T2-weighted MR images, revealing a cervical carcinoma with vaginal infiltration (A, B, arrows). Visualization by axial T2-weighted view (C, arrow) and DWI image (D, arrow) reveals left parametrial invasion—loss of the hyperintense cervical rim on the left lateral aspects of the cervix, with the irregular interface between the tumor and the parametrium. No pelvic adenopathy was noted

2.2 | Treatment

The patient's treatment plan was discussed during multidisciplinary conference, and she was subsequently referred for consultation with a radiation oncologist.

The patient was treated with pelvic EBRT. In order to spare the graft and the usual organs at risk (small bowel, bladder, and rectum), a volumetric-modulated arc therapy (VMAT) technique of an intensity-modulated radiotherapy (IMRT) plan was applied prior to the treatment (Figure 5). The prescribed total dose of EBRT to planning target volume (PTV) was 50 Gy delivered in 25 fractions of 2.0 Gy. The aim of the target coverage was to deliver at least 95 and 100% of the prescribed dose to the PTV and CTV, respectively. Treatment duration was 5 weeks. A mean dose of 12 Gy was delivered to the kidney. The EBRT has been followed by MRI-guided high-dose rate brachytherapy, delivering 30 Gy to 90% of the high-risk CTV (5 Gy per fraction, 2 fraction per week, totally 6 fractions). Implants were performed under general anesthesia in an operating room using MR imaging for brachytherapy planning (Figure 1).

Due to the immunosuppressed status of this patient, we elected to bypass concurrent chemotherapy with cisplatin or carboplatin in order to lessen nephrotoxicity and hematological toxicity.

2.3 | Outcome and follow-up

During the first 3-month follow-up after completing radiotherapy, the patient's pelvic MRI showed complete tumor clinical response (Figure 6). Her 6-month follow-up confirmed that the patient was in complete remission with no evidence of the disease. Her MRI revealed asymptomatic postradiation changes in the pelvic tissues, the ureter slightly dilated, and tortuous. Kidney function scores at this time were relatively normal: Urea level was 8.4 mmol/L, and creatinine level was 127.5 micromole/l.

3 | DISCUSSION

Among the gynecologic cancers, including uterine, cervical, vaginal, vulvar, and ovarian, the HPV-related cancers are known to increase among women who have undergone organ transplant as compared to women in the general population.[7,8] Several risk factors for post-transplantation cancer growth have been identified, and immunosuppression is considered to be the most important risk factor as it decreases the immunologic control of oncogenic viral infection and immunosurveillance.[8,9] Due to the fact that HPV-related cancers result from persistent infection with oncogenic HPV, it was hypothesized that maintenance immunosuppression to prevent graft rejection may contribute to reactivation of latent HPV infections, including high-risk oncogenic HPV types that may become persistent and eventually result in neoplasia and cancer.[10]

In the presented case, the patient was positive for high-risk HPV DNA, and she had been receiving immunosuppressive treatment for 9 years following kidney transplant and prior to being diagnosed with cervical cancer. According to the literature, locally advanced cervical cancer in this specific population is still quite rare, and most reports mention prevalence of HPV-associated cervical intraepithelial neoplasia or preinvasive lesions. This can be explained by the prolong preinvasive state of cervical cancer precursors and the close follow-up kidney transplant recipients receive. Due to the fact that HPV is a common infection in a kidney transplant recipient, and that most HPV cancers are preventable with screening and targeted therapies, careful follow-up is needed in this

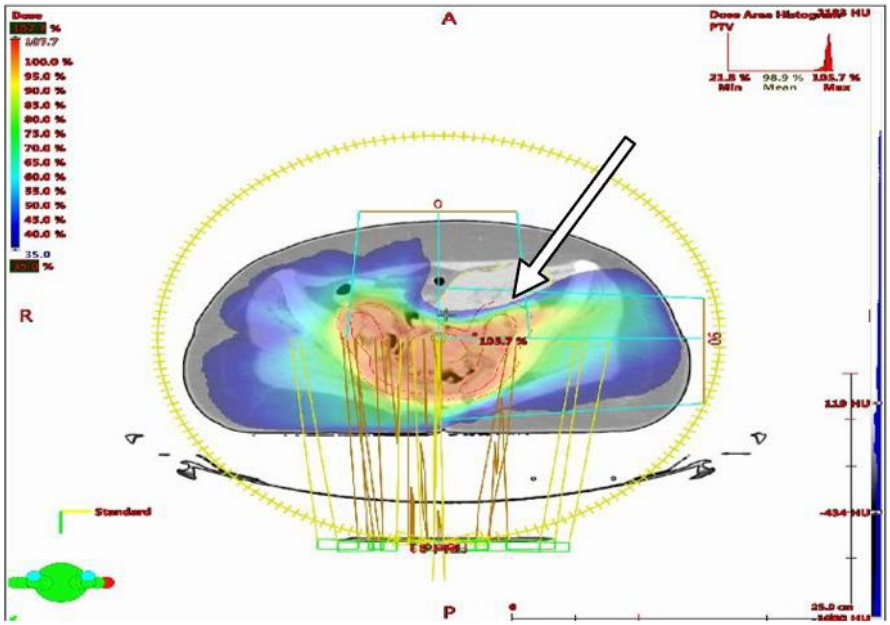

FIGURE 5 External beam plan using the intensity-modulated radiation therapy technique. Kidney graft on the left side (arrow) was cut off on the computed tomography scan, and beams could not be delivered to that side

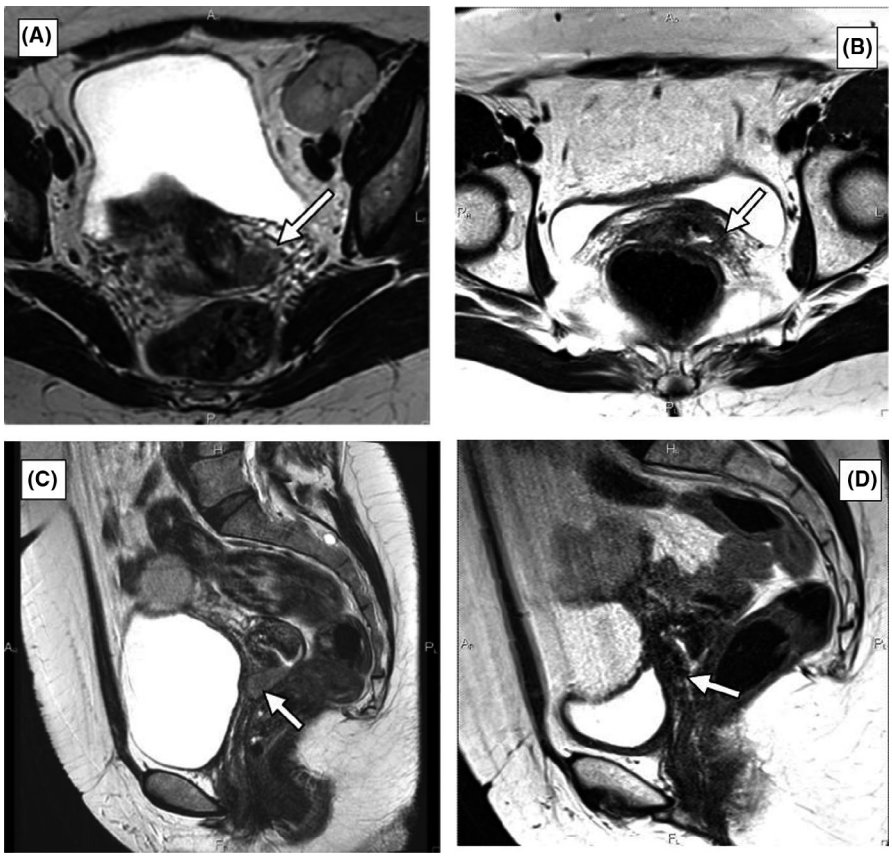

FIGURE 6 Post-treatment MRI shows complete tumor response when compared with the baseline study. Axial (A, B) T2-weighted MR images show IIB stage primary cervical tumor with parametrial invasion before treatment (arrow A) and no parametrial extension 3 mo after radiotherapy (arrow B). Sagittal (C, D) T2-weighted MR images show cervix tumor prior to (arrow C) and after (arrow D) the treatment—cervix is contracted with no evidence of disease 3 mo after the finish of radiotherapy

category of patients.[9,11] Some clinicians recommend more frequent screening of immunocompromised women (such as kidney transplant recipients) if high-risk HPV DNA is detected (every 6 months instead of annual visits). Some authors mention the ideal option for preventing HPV infection and disease would be using pretransplant prophylactic HPV vaccination of age-eligible kidney transplant recipients.[11]

Concurrent chemoradiation followed by brachytherapy is currently the standard of care treatment for locally advanced cervical cancer.[1,2] However, the use of radiation therapy, both external beam and brachytherapy, for cervical cancers presents definite issues for transplant recipients. The placement of the transplanted kidney often presents a risk for damage from radiotherapy that is essential for gynecological cancers that develop post-transplant. Despite these challenges, the literature supports the safety and efficacy of radiation therapy in kidney allograft recipients with locally advanced cervical cancer.[3-6] However, the available publications are mostly limited to case reports and case series, so oncologic outcomes and treatment toxicity have yet to be well studied using broader clinical data as compared to those in the nontransplant population.

Few options are traditionally explored to adapt radiation therapy in patients with organ transplants, such as modification of dose or radiation field to minimize irradiation of an allograft to avoid graft loss. When technically possible, moving the allograft out of the field of radiation is another option to protect it.[7,12,13]

Radiation therapy must be carefully planned to assure efficacious local and regional control of tumor regrowth.[14,15] One of the most challenging tasks in our case was to enhance gross target volume delineation to improve targeting and local tumor control and to reduce radiation dose to surrounding tissues, especially for the allograft. For these purposes, VMAT technique of IMRT was employed. This technique has the ability to modulate the intensity of the radiation beam to deliver an increased dose to target tissue and a reduced dose to healthy tissues that resulted in better local control of the primary tumor, as well as less radiation injury to normal surrounding tissue.[16-18] For brachytherapy, as a part of the standard treatment of advanced stages of cervical cancer, CT and MR imaging–compatible applicators were used to confirm accurate positioning, reduce insertion-associated complications, and enhance tumor delineation with 3D techniques.

4 | CONCLUSIONS

Our patient's case provides evidence that radiation to the modified pelvis using new the VMAT technique of IMRT followed by brachytherapy, while avoiding the renal allograft, is technically feasible and ensures adequate target volume while reduces side effects. Nevertheless, given the uniqueness of the problem, the treatment of such patients should be strictly individualized and carried out in reference

radiology centers with the availability of high-precision modern radiation therapy technology and well-trained personnel.

Future studies in the management of advanced cervical cancer patients following organ transplantation will be required to adapt standard treatment protocols to potential risk factor such as organ and age of transplant, type of immunosuppressive therapy, and potential use of new treatment approaches such as immunotherapies.

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The authors thank the patient for granting permission to publish her information.

CONFLICT OF INTEREST

The authors report no conflict of interests to declare.

AUTHOR CONTRIBUTIONS

OM: identified the patient, and wrote and edited the manuscript. AS: provided the clinical and radiological data. VS managed the treatment of the patient. PP: provided the histopathological data. SM: edited the manuscript. All authors: have read and approved the final version of the manuscript.

ETHICAL APPROVAL

We have reported this case in compliance with the Declaration of Helsinki. Written informed consent was obtained from the patient to publish her case details (including images).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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