



HPV-independent cervical cancer associated with non-reducible pelvic organ prolapse: A case report

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1. Introduction

Greater than 90% of cervical cancers are caused by infection with human papillomavirus (HPV) (Xing et al., 2020). Despite significant advances in the prevention of cervical cancer through screening tests and HPV vaccination, cervical cancer remains the fourth most common cancer in females worldwide, with 604,000 new cases and 342,000 deaths in 2020 (Sung et al., 2021). Pelvic organ prolapse (POP) is also very common, with the reported lifetime risk of undergoing surgery for POP in the United States at 12.6% (Wu et al., 2014). Although cervical cancer and pelvic organ prolapse are both common, the presence of concomitant cervical cancer and POP is rare as described in a recent meta-analysis (Nicholson et al., 2021). In this report, we present a case of HPV-negative cervical cancer associated with non-reducible uterine procidentia.

Case presentation

An 81-year-old G3P3003 presented to an OBGYN clinic for symptoms related to POP including significant pain and bleeding. She denied bowel or bladder symptoms. She reported prolapse symptoms for many years, but had significant worsening over the past three months. She had no known medical history, and had not received medical care in over 50 years for religious reasons. She had three prior vaginal deliveries, and never received cervical cancer screening. At the clinic visit, she was noted to have complete procidentia with a 6 cm ulcerated mass replacing the cervix. The mass was biopsied and returned invasive well to moderately differentiated squamous cell carcinoma, p16

immunostain negative. Reduction of the prolapse was attempted in clinic but was unsuccessful. She underwent PET/CT which demonstrated severe pelvic prolapse with a large mass replacing the cervix and surrounding vaginal enhancement extending into the paravaginal soft tissues concerning for locally invasive disease (Fig. 1). There was no evidence of distant metastasis.

Shortly after this visit, she developed new purulent drainage from the mass. She was seen by a primary care physician, and was sent to the Emergency Department where she was found to have polymicrobial superinfection of the necrotic cervical mass. She was admitted to the hospital, started on broad-spectrum antibiotics, and gynecologic oncology was consulted. A second attempt was made to reduce the prolapse at the bedside which was unsuccessful. After review of imaging and thorough physical exam, she was found to have at least stage IB3 cervical cancer (Fig. 2). She was discharged home on oral antibiotics.

After multidisciplinary discussion including gynecologic oncology, radiation oncology, and urogynecology, a plan was made to proceed with primary surgical management with attempted reduction under anesthesia followed by exploratory laparotomy, radical abdominal hysterectomy, and bilateral salpingo-oophorectomy followed by likely adjuvant chemoradiation therapy given the extent of bulky disease. If unable to reduce the prolapse under anesthesia, the plan was to perform a combined vaginal and abdominal surgical approach with urogynecology, followed by apical suspension or possible anterior repair, posterior repair, or perineorrhaphy as needed.

Two weeks later, the patient underwent surgery as scheduled. Once

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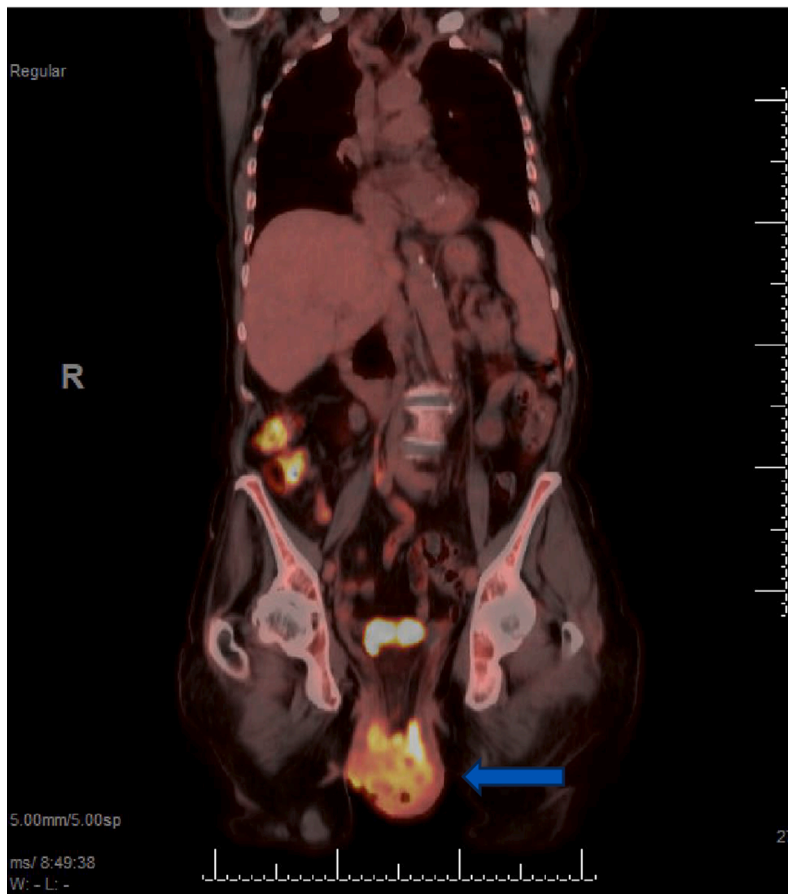
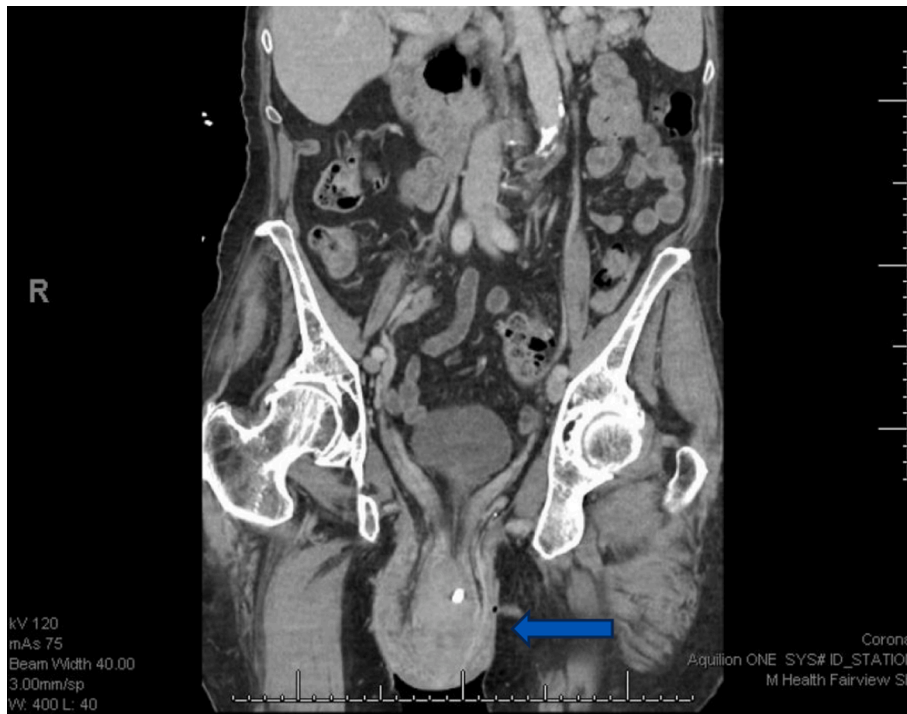


Fig. 1. A) Computed tomography scan at the time of diagnosis with proctocolitis and cervical mass present (blue arrow) and B) positron emission tomography demonstrating fludeoxyglucose-18 avidity of the cervical mass (blue arrow).

the patient was under anesthesia, the prolapse was only able to be partially reduced. A vertical midline incision was made, and the abdomen and pelvis were explored with no evidence of metastatic disease. However, there was complete obliteration of the rectovaginal space concerning for tumor erosion into the posterior vagina and perirectal tissues. There was thickening in the right parametria concerning for tumor invasion versus chronic infection given some pockets of purulent material that were encountered in this area. Given concern for involvement of the posterior vagina and perirectal tissues as well as inability to safely resect the uterus given non-reducible prolapse, the decision was made to perform a rectosigmoid resection. The uterus, cervix, upper vagina, and rectum were removed en bloc (Fig. 3), and an end colostomy was created with a Hartmann's pouch. There was only 3 cm of vaginal length remaining at the end of the hysterectomy. No further prolapse procedures were performed given the short vaginal length and no evident prolapse after cuff closure. Given the PET was negative for metastatic disease and adjuvant radiation was planned, lymphadenectomy was not performed. Cystoscopy was then performed which showed a diffusely inflamed bladder without obvious tumor, but there was a suspicious hypervascular area that was biopsied. The total blood loss was 1 L. On the final pathology report, the mass was a well-differentiated invasive squamous cell carcinoma measuring 5.6 cm involving the vagina, cervix, and myometrium. The rectum was negative for malignancy, and all mesorectal lymph nodes were negative. The margins were all negative, but the posterior margin of paracervical adipose tissue was less than 1 mm. The bladder biopsy was negative. The final surgical stage was IIA2. HPV PCR testing was performed after total cellular DNA extraction and DNA amplification and was found to be negative.

Her immediate post-operative course was complicated by acute

kidney injury, lactic acidosis, and persistent leukocytosis. She was treated with IV antibiotics and normal saline with significant improvement. Her colostomy was functioning appropriately, and she was voiding spontaneously. She was discharged home after 6 days in the hospital. Over the next few weeks, she was re-admitted twice for post-operative fevers, and during both admissions had a negative infectious work-up and was ultimately discharged home. At her post-operative clinic visit, she was doing well with normal colostomy and bladder function. She met with radiation oncology, and she received adjuvant chemoradiation with weekly cisplatin and 5040 cGy in 28 fractions. They did not plan to pursue high dose rate brachytherapy given her short residual vagina. She tolerated chemoradiation well with no grade 3 or higher toxicities.

2. Discussion

Treatment for cervical cancer primarily depends on the stage of disease at the time of diagnosis, with the recommendation that those with early-stage disease be treated with surgical management and those with locally advanced disease undergo primary chemoradiation (Koh et al., 2019). Surgery is generally avoided in locally advanced disease due to concerns regarding the frequency with which adjuvant radiation is required to treat residual disease and the significant morbidity associated with radiation after surgery. However, the presence of irreducible pelvic organ prolapse makes treatment planning more complicated.

A systematic review by Matsuo and colleagues reported on patients with cervical cancer complicated by POP (Matsuo et al., 2016). In this review of 78 included cases, the majority of cervical cancers were stage I (56%) although stage II-IV cancers were also included. There was a wide range of treatment modalities described, with most patients either being treated with radiation alone (38.5%) or surgery alone (33.3%), although



Fig. 2. Non-reducible uterine prolapse with cervical mass prior to surgery. Cervical os identified by black arrow.

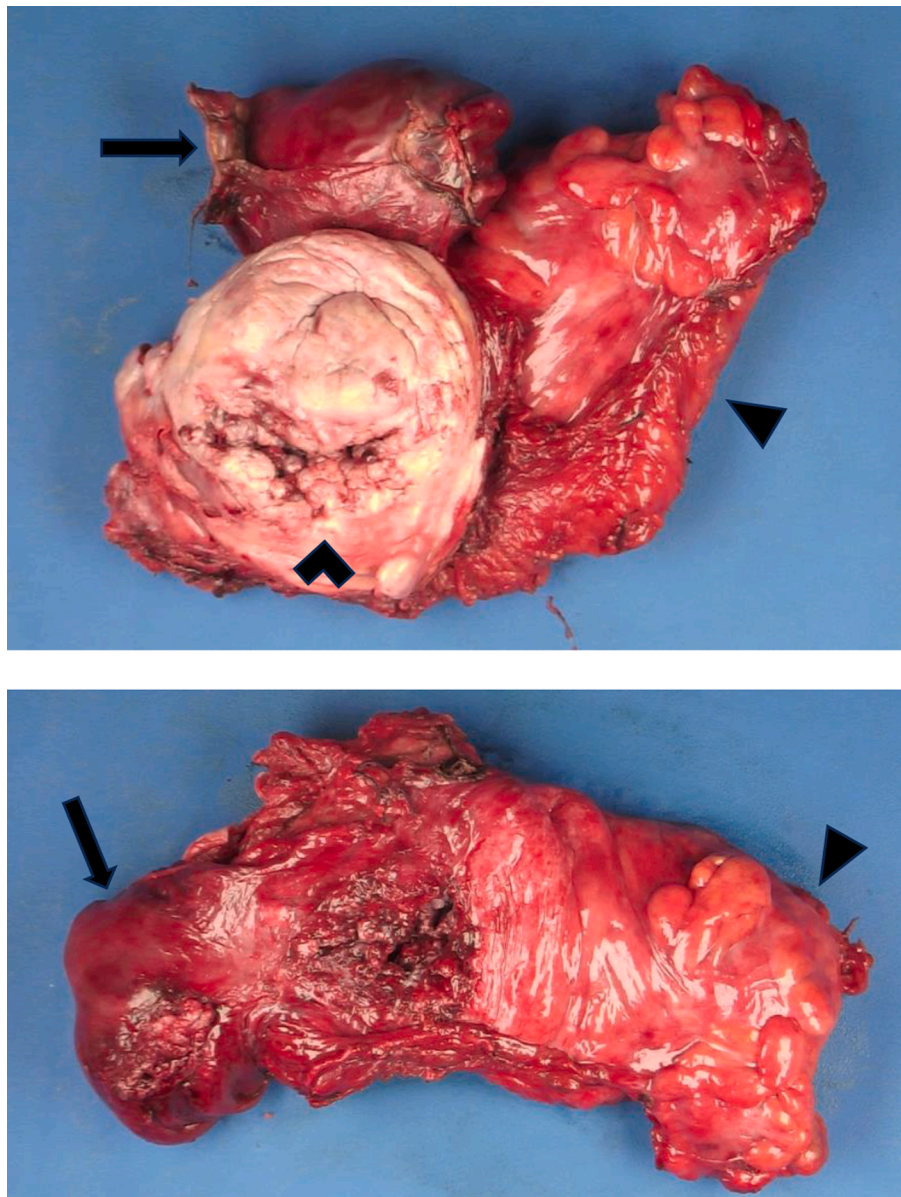


Fig. 3. Surgical specimen including uterus (black arrow), cervix (chevron), upper vagina, and rectum (triangle).

some patients were treated with surgery followed by radiation (16.7%) or radiation followed by surgery (11.5%). The patients in this review underwent varying types of surgery and radiation therapy, highlighting the lack of a standardized approach. While they do report that the patients who underwent surgery with or without radiation therapy had improved disease-specific overall survival than those who underwent radiation alone, this conclusion is limited by the small sample size, variety in stage of disease and treatment method, as well as the retrospective nature of the study.

Primary chemoradiation would generally be the recommended treatment for our patient with stage II cervical cancer according to guidelines (Koh et al., 2019). Successful treatment with primary radiation in patients with POP has been described in case reports (Dawkins et al., 2018; Jacomina et al., 2021; Reimer et al., 2008). In two of these case reports describing patients with stage IIA2 and IIIC1 disease, the prolapse was first reduced and a pessary was used to maintain prolapse reduction during radiation therapy (Dawkins et al., 2018; Jacomina et al., 2021). While there are concerns regarding uterine mobility affecting this approach, these reports suggest it is a viable treatment option. When the prolapse is not reducible, primary radiation has still

been used successfully, particularly in patients with significant comorbidities and bulky disease (Reimer et al., 2008). Reimer and colleagues used radiation followed by total vaginal hysterectomy and colpocleisis in a patient with stage IIA disease with no cancer or prolapse recurrence at 5 years (Reimer et al., 2008). However, this is generally not recommended due to concern for increased risk of visceral injury and fistula formation (Matsuo et al., 2016). Given the inability to reduce our patient's prolapse, superinfection, and the effect of non-reducible prolapse on the patient's quality of life, primary surgical management was chosen.

Among the reported cases that were managed surgically, the most common surgical approach was vaginal hysterectomy (Matsuo et al., 2016; Kahn et al., 2020). While not routinely used for cervical cancer treatment, the radical vaginal hysterectomy has been described in the literature and was initially described for the treatment of cervical cancer (Sonoda and Abu-Rustum, 2007). Patients with significant prolapse can be good candidates for this procedure, and in some cases it is necessary if the prolapse cannot be reduced and the uterus and cervix cannot be accessed abdominally (Chung et al., 2018). In general, the radical vaginal hysterectomy has been replaced with the abdominal radical

hysterectomy due to ability to perform pelvic lymphadenectomy through the same incision. In this case, the abdominal approach was necessary for adequate assessment of the patient's extent of disease and ultimately for complete debulking with en bloc rectosigmoid resection. There are no studies comparing outcomes between vaginal and abdominal radical hysterectomy in patients with prolapse. There is limited role for laparoscopic hysterectomy in these patients given the associated reduced disease-free and overall survival compared with abdominal hysterectomy (Ramirez et al., 2018).

This is a unique case of HPV-negative squamous cell carcinoma. The vast majority of cervical cancers are caused by HPV, and of the cervical cancers that are HPV-negative, most are adenocarcinomas (Xing et al., 2020). The role HPV plays in concomitant cervical cancer and prolapse is not well understood. A large observational study showed lower HPV infection rates in patients with POP compared to the rest of the population (Qiao et al., 2023). However, only one of the other case reports of cervical cancer in the setting of POP reported on HPV status, and this patient had HPV-associated squamous cell cervical cancer with a synchronous anal adenocarcinoma (Skret et al., 2021). The possibility of false HPV negativity in our patient should also be considered, which has been reported in the setting of latent HPV infection, non-high risk HPV infection, and inherent sensitivity of HPV testing methods (Xing et al., 2020). Overall, the authors encourage reporting of HPV status in further case reports to help elucidate the role HPV plays in cervical cancer in patients with POP.

Given the rarity of our patient's presentation, the authors also question the role prolapse may have played in the development of cancer. While some have proposed that prolapse may be protective against cervical cancer through the process of cornification and removing the cervix from the vagina's acidic environment, others propose that the presence of chronic irritation and inflammation from prolapse and even pessary use may increase the risk of cancer (Matsuo et al., 2016). Given the lack of other cervical cancer risk factors, it is reasonable to consider if chronic inflammation secondary to prolapse may have contributed to cancer development in this patient. However, further research is necessary to determine the pathogenesis of HPV-independent cervical cancers and the role chronic inflammation may play in this pathway.

In summary, due to the infrequent overlap of POP and cervical cancer as well as the wide variety of patient presentations, there is limited data to guide decisions around cancer treatment in these patients. In this case, we describe a patient with bulky, stage II disease that was incompletely reducible and treated with a multimodal approach including surgical management followed by adjuvant chemoradiation therapy. Although primary radiation therapy is the preferred treatment modality for stage II disease, there are rare clinical scenarios where this is not feasible and thus a more tailored approach is required. This highlights the importance of collaborative treatment planning with gynecologic oncology, urogynecology, and radiation oncology as well as shared decision making with patients in those who have concomitant cervical cancer and non-reducible pelvic organ prolapse.

3. Patient consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

CRedit authorship contribution statement

Sarah J Davidson: Writing – original draft, Conceptualization. **Dina El-Rayes:** Writing – review & editing. **Mahmoud Khalifa:** Writing – review & editing. **Cynthia S Fok:** Writing – review & editing. **Britt K Erickson:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [Britt Erickson is a member of the editorial board for Gynecologic Oncology Reports, but was not involved in the editorial review or the decision to publish this article. Britt Erickson is also on the advisory board to GSK, AstraZeneca, and Merck. These companies had no involvement in the development of this manuscript. The authors have no other conflicts of interest to disclose].

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