Chemoradiotherapy in a patient with locally advanced small cell neuroendocrine carcinoma of the cervix complicated by pelvic organ prolapse: A case report

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ABSTRACT

Background: The coexistence of cervical cancer and pelvic organ prolapse represents a rare clinical scenario. Small cell neuroendocrine histology likewise represents only 0.9–1.5% of all invasive cervical cancers. There is no consensus regarding the optimal management of patients with concomitant locally advanced cervical cancer and pelvic organ prolapse.

Case summary: The patient was a 32-year old woman with an 8-cm fungating cervical mass extruding from the introitus. Biopsy was consistent with small cell neuroendocrine carcinoma. Examination showed stage IIIC1 cervical cancer with stage IV pelvic organ prolapse. After manual reduction, a pessary was used to optimize target volume reproducibility during definitive chemoradiation. The patient was treated using cisplatin and etoposide chemotherapy with intensity modulated radiation therapy followed by intracavitary brachytherapy. The patient had no clinical evidence of disease and recurrence of symptomatic prolapse one year after treatment completion.

Conclusion: This is the first reported case of a cervical neuroendocrine carcinoma in a prolapsed uterus, and the youngest patient in literature to have concomitant cervical cancer and pelvic organ prolapse. The use of a pessary for optimizing target volume reproducibility during definitive chemoradiation is a viable option in managing this rare case scenario.

1. Introduction

Cervical cancer is the most common gynecologic malignancy worldwide, predominantly arising in women from developing countries. In 2018, there were approximately 570,000 cases and 311,000 deaths from cervical cancer globally, with an incidence of 13.3 per 100,000 women (Arbyn et al., 2020). Well-established guidelines pertain to the management of squamous cell carcinomas and adenocarcinomas, comprising the vast majority of invasive cervical cancers. Neuroendocrine carcinomas (NEC) account for only 0.9% to 1.5% of cervical cancers, with a recent increase due to better diagnosis (Angiolo et al., 2016; Gibbs et al., 2019). They typically have a more aggressive behavior, higher propensity for metastases, and poorer clinical outcomes (Salvo et al., 2019). Prospective data defining the standard management for cervical NEC are lacking. Treatment usually follows a multimodality approach, with surgical and radiotherapy techniques extrapolated from invasive cervical cancers and chemotherapeutic regimens from small cell cancers in other primary sites.

Pelvic organ prolapse (POP) in the setting of cervical cancer complicates clinical decision-making. Although varying degrees of symptomatic POP occurs in 1.5–9 women per 100 person-years and will develop in as much as 50% of women (Barber and Maher, 2013), the coexistence of POP and cervical cancer is rare largely because of their difference in age predilection. Cervical cancer incidence rises after the age of 25 years, with an average age at diagnosis of 53 years (Arbyn et al., 2020). Likewise, the mean age at diagnosis for cervical NEC is 48.1 years (Gibbs et al., 2019). On the other hand, the peak incidence of symptomatic POP occurs between ages 70 and 79 years (Barber and...
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coital bleeding and intermittent spotting. Two months prior to consul-
parametrial involvement.
Financial limitations. On chest and abdominal CT, the lungs, liver, and
visualized bones were negative for metastases. There were no para-
reproducible target volume coverage while minimizing irradiation to
adjacent normal tissues. As we have hypothesized that the prolapse was
primary to progressive tumor enlargement, any surgical intervention
was reserved in the event of intractable or recurrent prolapse should it
persist despite significant tumor shrinkage.
Prior to RT treatment planning, a #9 Gellhorn pessary (3.75 in.
diameter) was inserted. The patient was fitted with an alpha cradle for
immobilization. The diagnostic abdominopelvic MRI was co-registered
with the CT simulation images for guidance in target delineation,
albeit with some limitations because the patient had no pessary inserted
during the MRI. Treatment planning was done using Philips Pinnacle
version 9 (Fitchburg, WI, USA). The clinical target volume (CTV) was
defined as the gross tumor, cervix and uterus, adnexa, superior half of
the vagina, parametria, pelvic nodes, and para-aortic lymph nodes.
Currently, there is no consensus on the clinical benefit of routine pro-
phylactic para-aortic nodal RT in cervical NEC; but we have decided to
use an extended field technique based on the aggressive histology and
the pelvic nodal involvement despite the increased risk for gastrointes-
tinal and/or hematologic toxicities. The planning margins consisted of 5
mm around the nodal regions, 8 mm around the parametria and vagina,
and 12 mm around the cervix and uterus. An additional 20 mm was
added to the inferior margin to account for the prolapse. An intensity-
modulated RT plan was designed with 7 coplanar fields of 6-MV

2. Case presentation

The patient is a 32-year old gravida 5 para 4 (4014) with a 1-year
history of increasingly prolapsing vaginal mass associated with post-
coital bleeding and intermittent spotting. Two months prior to consul-
tation, she had incomplete bladder emptying, straining on urination,
and moderate hypogastric pain. Her medical history was unremarkable.
Physical examination revealed a uterine procidentia with a large, fun-
gating 6-cm cervical mass extending to the cervico-vaginal junction
(Fig. 1A). Biopsy showed poorly differentiated carcinoma. Further
immunohistochemical stains revealed synaptophysin (+), chromogranin
(+), and CD56 (+), consistent with a diagnosis of small cell neuroen-
docrine carcinoma. The mass was then manually reduced into the
vaginal canal (Fig. 1B). Rectovaginal examination was negative for
parametrial involvement.
An abdominopelvic MRI revealed a cervical mass measuring 7.4x6.6
cm with prolapse of the cervix and inferior portion of the uterus into the
vaginal canal. There were mild dilatations of bilateral pelvocalyceal
systems and proximal ureters secondary to the prolapse of the distal
ureters and inferior portion of the urinary bladder. The mildly enlarged
iliac lymph nodes, largest measuring 1.1 cm, were considered clinically
node positive (Fig. 2). No histologic confirmation of nodal status was
made, following the diagnostic algorithm provided by Salvo et al. (Salvo
et al., 2019) A positron emission tomography (PET) scan is the preferred
modality for staging cervical NEC; however this was not done due to
financial limitations. On chest and abdominal CT, the lungs, liver, and
visualized bones were negative for metastases. There were no para-
aortic, mediastinal, or supraclavicular lymphadenopathy. Baseline
organ functions were within normal limits. Using the International
Federation of Gynaecology and Obstetrics (FIGO) 2018 staging for cer-
vical cancers (Bhatla et al., 2018), the patient was clinically staged as
IIIC1r with a concomitant Pelvic Organ Prolapse Quantification (POP-Q)
stage IV prolapse (Aa + 2, Ba + 5, C + 8, Ap 0, Bp 0, gh 4, pb 2.5, tvl 9)
(Madhu et al., 2018).
There were several treatment challenges posed by the unique disease
presentation of our patient. First, the patient had locally advanced cer-
vical NEC; and the treatment consensus of the multidisciplinary team,
composed of a radiation oncologist, gynecologic oncologist, and uro-
logic gynecologist, was concurrent chemoradiation (Salvo et al., 2019;
Gardner et al., 2011; National Comprehensive Cancer Network, 2021).
Second, the uterine prolapse had to be reduced and kept in a constant
position throughout the duration of external beam radiotherapy (RT). If
the prolapse is only manually reduced into the vagina, there can be
significant inter-fractiol motion, necessitating larger treatment mar-
gins. There is also a risk of recurrent prolapse needing repeated re-
ductions. Aside from the discomfort and inconvenience, this increases
the risk for injury, infection, and treatment interruption. We therefore
agreed to use a vaginal pessary to restore pelvic anatomy and keep the
prolapse reduced during the entire RT duration to ensure adequate and
reproducible target volume coverage while minimizing irradiation to
adjacent normal tissues. As we have hypothesized that the prolapse was
secondary to progressive tumor enlargement, any surgical intervention
was reserved in the event of intractable or recurrent prolapse should it
persist despite significant tumor shrinkage.

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Fig. 1. Uterine prolapse with cervical mass A) on presentation, and B) after manual reduction.
photons, optimized to maintain planning target volume (PTV) coverage and normal organ sparing (Fig. 3A). The RT plan was intended to deliver a prescription dose of 50 Gray (Gy) to the PTV, divided into 2-Gy daily fractions for five days a week. Of note, the pessary was included in the PTV. Because of its silicone material however, it was not expected to cause differential attenuation of the photon beam and alter the surrounding dosimetry significantly.

After receiving 12 fractions, the patient expressed moderate to severe pelvic pain with difficulty urinating and passing stools secondary to the #9 Gellhorn pessary. Upon reassessment, the cervical tumor had markedly decreased in size, from 9 cm to 4 cm. A #5 ring pessary (3 in. diameter) was inserted; and the patient underwent repeat CT simulation and target delineation. A new RT plan was made to adapt to the reduced target volumes (Fig. 3B).

Upon completion of external beam RT, the ring pessary was removed because of mild to moderate pelvic discomfort. The patient had a 3-cm smooth, and nodular cervix in its normal pelvic location showing good response to treatment. We proceeded with intracavitary high-dose-rate (HDR) brachytherapy using an Iridium-192 source in a remote after-loading technique. A dose of 6.5 Gy in 4 bi-weekly fractions was delivered to point A using an intrauterine tandem and ovoids. The cervix received a total equivalent dose in 2-Gy fractions (EQD2) of 86 Gy using an $\alpha/\beta$ of 10.

Based on recommendations from published data on neuroendocrine carcinomas of the cervix (Salvo et al., 2019; Gardner et al., 2011, National Comprehensive Cancer Network, 2021), the patient received concurrent cisplatin (60 mg/m$^2$) on day 1 and etoposide (100 mg/m$^2$) on days 1–3 delivered every 21 days for a total of four cycles, three cycles during and one after RT. She tolerated the treatment well without significant adverse effects and treatment interruptions. No succeeding intervention was done to address the uterine prolapse aside from the insertion of a pessary during RT. On follow-up one year after treatment completion, the patient is well and has clinically no evidence of disease. She likewise has no recurrence of symptomatic pelvic organ prolapse.

3. Discussion

The World Health Organization (WHO) classifies cervical NEC into low-grade (carcinoid and atypical carcinoid tumor) or high-grade (small-cell and large-cell), the small-cell type being the most common histology (80%) (Angiolo et al., 2016). Unlike cervical squamous cell carcinomas and adenocarcinomas, NEC has a rapidly progressive course and leads to widespread hematogenous metastases despite aggressive local and systemic therapy. Overall, the 5-year survival rate is 36% and the median survival ranges between 22 and 25 months (Salvo et al., 2019). The Society of Gynecologic Oncology (SGO) recommendation for locally advanced NEC (i.e. FIGO 2018 stages IB3, IIA2, IIIA-C, and IVA) is a combination of RT and four to six cycles of platinum and etoposide.
chemotherapy (Gardner et al., 2011). Likewise, the National Comprehensive Cancer Network (NCCN) recommends either primary chemoradiation with or without adjuvant chemotherapy or neoadjuvant chemotherapy followed by chemoradiation, with preference to the former (National Comprehensive Cancer Network, 2021). Because of the paucity of data, there is no level I evidence to show that one approach is superior to the other.

The coexistence of cervical cancer and POP represents a rare clinical scenario because of the difference in age predilection. POP is typically associated with pelvic floor dysfunction from increasing age, parity, vaginal delivery, chronic constipation, and connective tissue disease (Pelvic Organ Prolapse, 2019). However, in our patient without classical risk factors for POP, the prolapse was likely due to mass effect from the progressively enlarging cervical tumor. This hypothesis is strengthened by the resolution of the prolapse with tumoral response after treatment.

Treatment for cervical cancer in the setting of a uterine prolapse varies widely across literature. Most reported cases suggest acceptable clinical and functional outcomes with a radical vaginal hysterectomy with bilateral pelvic lymphadenectomy followed by adjuvant chemoradiation (Kahn et al., 2020). Matsuo et al. reported potentially better outcomes following surgery-based treatment with a 5-year survival of 77% compared to 68% in patients receiving RT alone (Matsuo et al., 2015). Considering the stages of both the malignancy and the prolapse, management is typically individualized in these rare case scenarios. Patients with complete uterine prolapse, bulky cervical tumors, pelvic lymphadenopathies, and aggressive histology, such as our patient, may not be ideal candidates for a primary surgical approach. Neoadjuvant chemotherapy to downsize the tumor prior to definitive local treatment is another feasible option. However, this was not the chosen approach as this could delay initiation of local therapy, which was disadvantageous for our patient with symptomatic POP. We proceeded with upfront chemoradiation to address the symptom burden and provide prompt local and systemic control of the aggressive malignancy.

The altered pelvic anatomy in a uterine prolapse is a challenging factor to consider in planning for primary curative RT. Reimer et al. treated a patient with stage IIA cervical SCC and irreducible procidentia using extracorporeal pelvic RT with weekly cisplatin followed by vaginal hysterectomy, partial colpectomy, and colpocleisis (Reimer et al., 2008). Kriplani et al. manually reduced the procidentia under sedation and kept the patient nonambulatory to facilitate the delivery of radiotherapy with the pelvic organs in situ (Kriplani et al., 1995). Reduction of the prolapse prior to RT was generally recommended in order to decrease the risk of visceral injury and the formation of vesicovaginal or rectovaginal fistulas (Matsuo et al., 2015). However, when reduced into the vaginal canal, the mobility of the prolapse limits the accuracy and reproducibility of the target volume position for daily RT. Dawkins et al. published the only reported case in which a vaginal pessary, together with perineoplasty, was done before chemoradiation in a 72-year old patient with cervical cancer and POP (Dawkins et al., 2018). We did a similar approach of using a vaginal pessary during RT but did not proceed with perineoplasty because of the resolution of symptomatic prolapse after treatment. We found this to be a viable option in patients intended for primary chemoradiation.

4. Conclusion

This is the first reported case of a cervical neuroendocrine carcinoma in a prolapsed uterus, and the youngest patient in literature to have concomitant cervical cancer and pelvic organ prolapse. Using a vaginal pessary during primary chemoradiation is a viable option in managing this rare case scenario.

Consent
Written informed consent was obtained from the patient.

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CRediT authorship contribution statement

Luisa E. Jacomina: Investigation, Writing - original draft. Michelle D. Garcia: Investigation, Writing - original draft. Andrea C. Santiago: Investigation, Methodology. Irene M. Tagayuna: Investigation, Methodology, Supervision. Warren R. Bacorro: Supervision, Writing - review & editing.

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.

References

Arbyn, M., Weiderpass, E., Bruni, L., et al., 2020. Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. Lancet Glob Heal. 8 (2), e191–e203. https://doi.org/10.1016/S1473-3099(19)30482-6.

Angiolo, G., Silvestro, C., Giovanni, A., 2016. Neuroendocrine tumors of the uterine cervix: a therapeutic challenge for gynecologic oncologists. Gynecol Oncol. https://doi.org/10.1016/j.ygyno.2016.12.003.

Gibbs, J., Mei, S., Economos, K., Lee, Y.C., Kanis, M.J., 2019. Clinicopathologic features, incidence, and survival trends of gynecologic neuroendocrine tumors: a SEER database analysis. Am J Obstet Gynecol. 221 (1), 53.e1–53.e6. https://doi.org/10.1016/j.ajog.2019.02.052.

Salvo, G., Martin, A.G., Gonzales, N.R., Frumovitz, M., 2019. Updates and management algorithm for neuroendocrine tumors of the uterine cervix. Int J Gynecol Cancer. 29, 986–995. https://doi.org/10.1136/ijgc-2019-000504.

Barber, M.D., Maher, C., 2013. Epidemiology and outcome assessment of pelvic organ prolapse. Int Urogynecol J Pelvic Floor Disfunct. 24 (11), 1783–1790. https://doi.org/10.1007/s00192-013-2169-9.

Kahn, R.M., Gordhandas, S., Craig, K., et al., 2020. Cervical carcinoma in the setting of uterovaginal prolapse: Comparing standard versus tailored management. Ecanermedicalsience. 14 (1043), 1–8. https://doi.org/10.3332/ECANCER.2020.1043.

Bhatia, N., Aoki, D., Sharma, D.N., Sankaranarayanan, R., 2018. Cancer of the cervix uteri. Int J Gynecol Obstet. 143 (Suppl. 2), 22–36. https://doi.org/10.1002/ijgo.12611.

Madhu, C., Swift, S., Moloney-Geany, S., Drake, M.J., 2018. How to use the Pelvic Organ Prolapse Quantification (POP-Q) system? Neurourol Urodyn. 37, S39–S43. https://doi.org/10.1002/nau.23740.

Gardner, G.J., Reidy-Lagunes, D., Gehrig, P.A., et al., 2011. Neuroendocrine tumors of the gynecologic tract: a Society of Gynecologic Oncology (SGO) clinical document. Gynecol Oncol. 122, 190–198. https://doi.org/10.1016/j.ygyno.2011.04.011. - 2011 National Comprehensive Cancer Network. Cervical Cancer (Version 1.2021). https://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf. Published 2021. Accessed June 28, 2021.

Pelvic Organ Prolapse, 2019. ACOG Practice Bulletin, Number 214. Obstet Gynecol. 134 (5), E126–E142. https://doi.org/10.1097/AOG.0000000000002359.

Matsuo, K., Fullerton, M.E., Morini, A., 2015. Treatment patterns and survival outcomes in patients with cervical cancer complicated by complete uterine prolapse: a systematic review of literature. Int Urogynecol J. https://doi.org/10.1007/s00192-015-2731-8.

Reimer, D., Sztanksy, A., Steppan, I., et al., 2008. Cervical cancer associated with genital prolapse—a brief review of the literature and long-term results of successful treatment with radiochemotherapy and surgery in a very frail patient. Eur J Gynaecol Oncol. 29 (3), 272–275.

Kriplani, A., Relan, S., Kumar, L., Biswal, B.M., Rath, G.K., 1995. Incarcerated Procidentia: A Rare Complication of Carcinoma Cervix. Aust New Zeal J Obstet Gynaecol. 35 (4), 463–464. https://doi.org/10.1111/j.1479-828X.1995.tb02170.x.

Dawkins, J.C., Lewis, G.K., Toy, E.P., 2018. Cervical cancer complicating pelvic organ prolapse, and use of a pessary to restore anatomy for optimal radiation: A case report. Gynecol Oncol Reports. 26, 14–16. https://doi.org/10.1016/j.gore.2018.08.004.