



Case report

Isolated subcutaneous recurrence of high-grade neuroendocrine tumor of the cervix

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1. Background

Neuroendocrine carcinomas of the uterine cervix (NECC) are rare, accounting for less than 1% of cervical carcinomas. These tumors more commonly affect premenopausal women, and have been noted to be associated with high-risk HPV infections (Castle et al., 2018). Patients most often present with vaginal bleeding or with an abnormal pap smear. The World Health Organization recommends classifying neuroendocrine neoplasms as either low grade, including carcinoid or atypical carcinoid, or high-grade, including small cell and large cell neuroendocrine carcinomas. The majority of NECC are high grade neuroendocrine carcinomas that are aggressive tumors with a higher incidence of lymphovascular space invasion, lymph node metastasis, distant metastasis and extra-pelvic recurrence when compared to squamous and adenocarcinoma of the cervix (Zhu et al., 2019; Kurman, 2014; Abdallah et al., 2016; Gadducci et al., 2017). Due to their predilection for advanced disease, the five-year survival of all comers with NECCs is significantly lower than the overall five-year survival of squamous and adenocarcinoma of the cervix at 30% and >65%, respectively (Tempfer et al., 2018).

Histologically, neuroendocrine carcinomas can show solid or nested architecture, trabecular, or pseudoglandular and rosette-like architecture. While the cells of small cell neuroendocrine carcinoma show scant cytoplasm and inconspicuous nucleoli, large cell types demonstrate abundant cytoplasm, coarse chromatin, and prominent nucleoli. Immunohistochemistry demonstrates positivity with at least one neuroendocrine marker, of which, chromogranin, synaptophysin and CD56 are the most commonly utilized (Zhu et al., 2019; Tempfer et al., 2018).

In this report, we present an isolated recurrence of neuroendocrine tumor in the subcutaneous tissue, fourteen years following initial diagnosis. The patient being discussed has expressed explicit consent to

publish the details of their case.

2. Case report

A 30-year-old female presented with an abnormal pap smear in 2006. A loop electrosurgical excision procedure (LEEP) procedure demonstrated mixed adenocarcinoma and neuroendocrine tumor and the patient ultimately underwent a radical hysterectomy and pelvic lymph node dissection. Pathology reported a 2 × 0.9 × 0.8 cm large cell neuroendocrine tumor involving the cervix with two positive lymph nodes. One positive right parametrial lymph node involved a 0.4 cm metastatic tumor and one left pelvic lymph node involved a 1 cm focus of carcinoma. The patient underwent multi-modal therapy with etoposide and cisplatin chemotherapy and definitive pelvic radiation, followed by three cycles of carboplatin and paclitaxel. She had no evidence of disease at the end of treatment.

In 2010, the patient underwent laparoscopic bilateral salpingo-oophorectomy for isolated recurrence to the right ovary. Histology demonstrated poorly differentiated neuroendocrine carcinoma, staining positive for chromogranin, synaptophysin, BER-EP4, CK7, and p16, involving the ovary and fallopian tube. No additional systemic therapy was given at that time.

The patient continued to follow up with routine CT scans and pap smears which showed no evidence of disease for six years. In 2016, CT showed evidence of new peritoneal implants concerning for recurrence. PET scan confirmed the presence of three new FDG avid lesions, the largest being 1.4 cm in the left lateral pericolic gutter and two smaller intraperitoneal nodules on the right anterior abdominal wall. The patient underwent exploratory laparotomy, excision of peritoneal implants, and omentectomy with resection of all gross tumor. Pathology confirmed recurrent high-grade neuroendocrine carcinoma within the large pericolic implant and the omentum. The smaller anterior

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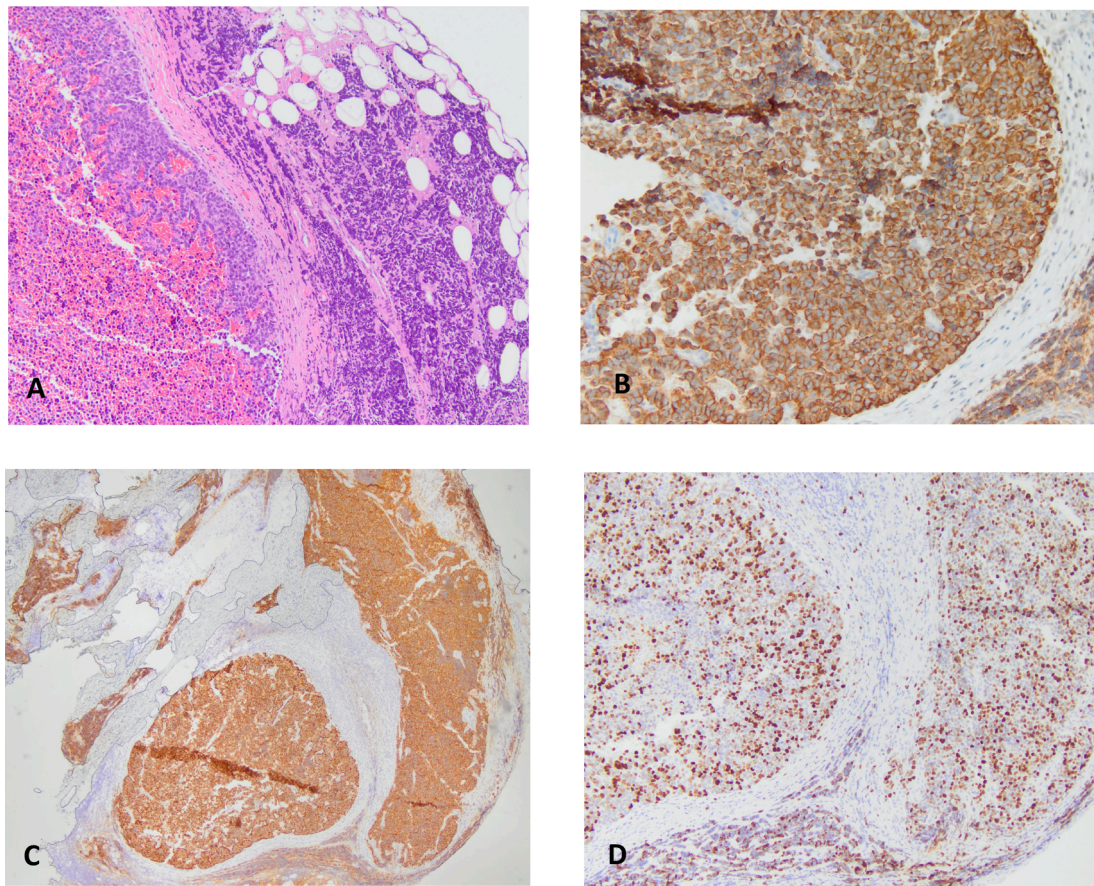


Fig. 1. Metastatic neuroendocrine carcinoma, large cell type (H&E) with abundant cytoplasm and prominent nucleoli (A); Chromogranin (B); Synaptophysin (C) and Ki-67 (D).

abdominal wall lesions and pelvic washings were negative for malignancy. The patient received three additional cycles of systemic chemotherapy with cisplatin and etoposide for recurrence of neuroendocrine carcinoma.

Follow up CT and PET scans showed two right sided nodules, felt to be stable in size, with the larger measuring 7 mm and increasing in FDG uptake. Given the concern for persistent disease, three additional cycles of etoposide and cisplatin were recommended. However, the patient strongly desired a chemotherapy holiday. The disease was monitored with CT scans and chest x-rays every three to four months, which showed slow growth of the two nodules from 7 and 4 mm to 15 and 9 mm, respectively, over eighteen months. The patient desired continuation of chemotherapy holiday throughout this interval. She was, however, amenable to an exploratory laparotomy with excision of these nodules, which was performed 23 months following the last chemotherapy cycle. Pathology showed recurrence of high-grade neuroendocrine carcinoma. A post-operative PET scan showed absence of FDG avid disease.

The patient then resumed surveillance visits with CT scan and physical exams at three-month intervals and remained without evidence of disease for 18 months. Of note, due to concern for exposure during the beginning of the coronavirus pandemic, surveillance visits were conducted via telemedicine. In August 2020, the patient presented with complaints of a mobile, “pea-sized nodule” in the subcutaneous tissue approximately 3 inches to the right of the umbilicus that was not associated with a prior incision. CT scan was unable to detect the lesion.

Excision of the 0.3 cm nodule and surrounding adipose tissue was performed in October 2020. Pathologic examination showed involvement by high-grade neuroendocrine carcinoma, large cell type. The tumor was predominantly solid with associated necrosis, and foci of

pseudoglandular and rosette-like formation. Cells with abundant cytoplasm, coarse chromatin and prominent nucleoli, showed strong diffuse staining with synaptophysin, chromogranin, and p16. Immunohistochemistry for Ki-67 highlighted the high proliferative rate in the tumor cells (Fig. 1). The tumor was compared to the previously resected peritoneal nodules and omentectomy from 2016 and showed similar morphology.

Follow up PET scan showed FDG avidity in the region of the subcutaneous nodule, which was felt to represent inflammation, given confidence of complete removal by the surgical team (Fig. 2). No other FDG avid lesions were identified. The patient recovered well from surgery and continues to be asymptomatic while resuming surveillance visits at 3-month intervals. The patient has remained on chemotherapy holiday since October 2016.

3. Discussion

NECC is a rare and aggressive form of cervical cancer. The most common sites of recurrence for NECC are the lungs, liver, and peritoneum. This is the first known reported case of an isolated recurrence to occur in the subcutaneous tissue not involving a prior incisional site. Additionally, this patient has undergone multiple successful surgical resections of solitary recurrences of NECC with relatively long disease-free intervals between each surgery.

Due to the rarity of the tumor, there is minimal literature available to guide treatment for these patients, creating a challenge for providers. The National Comprehensive Cancer Network (NCCN) and Society of Gynecologic Oncology (SGO) agree with multimodal treatment regimen for early stage and locally advanced disease. The use of chemotherapy, most often a platinum-based regimen and etoposide, has been widely



Fig. 2. PET scan with FDG avid region in right anterior abdominal wall.

adopted for treatment of NECC. However, these guidelines are extrapolated from data involving patients with small cell carcinoma of the lung as there is limited primary data involving patients with neuroendocrine carcinoma of the uterine cervix (Tempfer et al., 2018; Frumovitz, 2016). The use of surgery and pelvic radiation has shown mixed results in early stage (I-IIA) disease (Salvo et al., 2019).

In the primary treatment of locally advanced disease, such as this case, SGO recommends a combination of chemotherapy and radiation. A retrospective study of patients with advanced small cell NECC found that a combination of radiation with a total of at least five cycles of chemotherapy was associated with a greater 5-year disease free survival (62.5% vs 13.1%, $p = 0.025$) and improved overall survival (75% vs 16.9%, $p = 0.016$) (Wang et al., 2012). Despite the high rate of recurrence, there is an overall paucity of data to support an ideal therapy for recurrence of NECCs. A regimen of topotecan, paclitaxel and bevacizumab has also been noted to be effective in patients with recurrent NECC (Frumovitz et al., 2017).

There have been a number of studies looking at the genetics of a small number of neuroendocrine tumors. Unfortunately, no single mutation has been identified as the catalyst for neuroendocrine malignant transformation. The most common mutation is tp53 which may be present in around 62% of neuroendocrine tumors (Xing et al., 2018).

PIK2CA, a common mutation observed in other HPV related cancers, was also commonly identified. Interestingly, RB1 was not found to be very frequent in these small studies, yet it is almost ubiquitously present in small cell carcinoma of the lung. It is notable that RB1 mutation was also present in the present case being discussed and may have played a role in its unusual course. As new developments in targeted therapy progress, the need for additional studies regarding the genetic make-up of these tumors continues to increase.

This case presents an interesting indolent course of high grade NECC. High grade neuroendocrine carcinomas are typically characterized by rapid recurrence and dissemination with short overall survivals after recurrence. This patient with large cell NECC is without evidence of disease 15 years after initial diagnosis, even in lieu of multiple recurrences that have been managed mostly with surgical resection alone. There continues to be a need for additional study regarding treatment of recurrent NECC, particularly regarding isolated recurrence remote from initial diagnosis. This case may provide reason to consider surgical treatment alone in appropriate candidates.

CRedit authorship contribution statement

Lia Bos: Conceptualization, Visualization, Investigation, Formal analysis, Writing - original draft. **Alison Goulder:** Writing - review & editing. **Lauren Prescott:** Writing - review & editing. **Mirna Podoll:** Investigation, Writing - review & editing. **Michael Frumovitz:** Writing - review & editing. **Alaina J. Brown:** Conceptualization, Visualization, 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.

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