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A Rare Case of Cervical Cancer: Small Cell Neuroendocrine Carcinoma

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Abstract

Small cell neuroendocrine carcinoma of the cervix (SCNECC) is an aggressive and rare malignancy accounting for less than 5% of cervical cancers. This case report discusses a 50-year-old woman presenting with vaginal discharge and spotting, later diagnosed with FIGO stage IIIc1 SCNECC. Histology confirmed HPV 18-associated small cell neuroendocrine carcinoma of the cervix, with imaging revealing pathological pelvic lymph nodes in the absence of distant metastasis . A multidisciplinary approach recommended chemotherapy and radiotherapy as the treatment strategy. The report underlines the diagnostic challenges, poor prognosis, and need for multimodal management while advocating for research into targeted therapies to improve outcomes.

Keywords: Small Cell Neuroendocrine Cervical Carcinoma; Cervical Cancer; Human papillomavirus; Imaging; Prognosis

Abbreviations

SCNECC - Small Cell Neuroendocrine Carcinoma of the Cervix.
FIGO - International Federation of Gynaecology and Obstetrics.
HPV - Human Papillomavirus.
HSIL - High-Grade Squamous Intraepithelial Lesion.
MRI - Magnetic Resonance Imaging.
CT - Computed Tomography.
PET - Positron Emission Tomography.
SCC - Squamous Cell Carcinoma.
WHO - World Health Organisation.
NECC - Neuroendocrine Cervical Carcinomas.
NEC - Neuroendocrine Carcinomas.
NET - Neuroendocrine Tumours.
MAPK - Mitogen-Activated Protein Kinases.
KRAS - Kirsten Rat Sarcoma viral oncogene homolog.
BRCA - Breast Cancer Gene.
PD-L1 - Programmed Cell Death Ligand 1.

Introduction

Cervical cancer is the second leading oncological cause of mortality in the female population. Interestingly, cervical neuroendocrine tumours represent a rare subset of cervical cancers, with small cell neuroendocrine tumours accounting for less than 5% of cervical cancers. Approximately 80% of cases are associated with the presence of high-risk human papilliomavirus (HPV) subtypes, particularly HPV 18. They are notorious for their aggressive nature, as most patients present with lymph node involvement and metastasis [1]. Consequently, such patients carry a poor prognosis, with a 5-year overall survival rate of 34% [2].

This report highlights the case of a 50-year-old woman presenting with vaginal discharge and spotting, who was found to have an enlarging necrotic cervical lesion. A diagnosis of a FIGO IIIc1 cervical small cell neuroendocrine tumour was made following cervical biopsies and imaging. A treatment plan involving the oncologists was recommended by the multidisciplinary team.

Case Presentation

A 50-year-old lady, previously healthy, presented at the outpatient clinic with a six-week history of foul-smelling vaginal discharge associated with persistent vaginal spotting. Smear history was normal up to the previous year.

Speculum examination revealed a necrotic cervical lesion, measuring approximately 2 cm. A cervical smear at the time demonstrated a high-grade squamous intraepithelial lesion (HSIL) on a background of necrosis.

Two weeks later, a colposcopy showed significant enlargement of the cervical lesion to around 7cm. Histological evaluation of the cervical biopsies demonstrated a small cell neuroendocrine carcinoma of the cervix. HPV testing also confirmed the presence of HPV 18.

A pelvic MRI of the pelvis showed a 6.5cm by 2.2cm cervical mass with co-existing bilateral parametrial invasion and pathological pelvic sidewall lymph nodes. The findings were thus consistent with a FIGO IIIc1 cervical malignancy. A CT scan of the thorax, abdomen and pelvis confirmed the presence of the known cervical malignancy and right iliac metastatic lymphadenopathy in the absence of distant metastasis.

The case was discussed at the multidisciplinary team meeting and the patient was referred to oncology for further management. A PET/CT confirmed the cervical malignancy with pelvic lymph node involvement. Following discussion with the patient it was decided to refer to the oncology team to further plane her management.

Upon review by the oncology team, it was decided to start chemotherapy immediately due to the aggressive nature of the tumour which was growing rapidly. She was given carboplatin and etoposide every 3 weeks for four to six cycles. After the sixth cycle she will be reassessed via MRI and PET-CT with a plan to start chemo-radiotherapy and brachytherapy after.

Discussion

Cervical cancer remains the second leading oncological cause of mortality among women worldwide. While squamous cell carcinoma (SCC) and adenocarcinoma are responsible for most cervical cancers, neuroendocrine cervical tumours constitute a rarer subset, accounting for 5% of all cervical cancers [1]. Essentially, neuroendocrine malignancies are derived from neuroectodermal tissue, which gives rise to neuroendocrine cells within the glandular and squamous cervical epithelium [3].

The World Health Organization (WHO) previously classified neuroendocrine cervical carcinomas (NECC) into low-grade and high-grade tumours. Essentially, grade 1 and grade 2 neuroendocrine tumours (identical to typical and atypical carcinoid tumours respectively) were considered as low-grade, whereas small cell and large cell neuroendocrine tumours were regarded as high-grade [4].

However, the revised WHO classification (2020) now categorises NECC into two main groups, comprising of neuroendocrine tumours (NET) and neuroendocrine carcinomas (NEC), the latter referring to small cell and large cell neuroendocrine carcinomas [5]. Incidentally, small cell neuroendocrine carcinoma (SCNECC) is considered the commonest subtype. Although SCNECC can occur throughout the female reproductive system, they convey a propensity for the cervix [6]. Mixed neuroendocrine carcinomas may also occur, particularly when each of the two co-existing malignancies comprise at least 10% of the tumour composition. This may also include cases of co-existing SCC and adenocarcinoma [3].

Several studies highlight the significant association between SCNECC and human papillomavirus (HPV). The presence of high-risk HPV serotypes, particularly HPV 18, was detected in 80% of cases of SCNECC [1]. This underlines the importance of cervical screening and HPV typing in reducing the prevalence of such a disease. In this case report, the co-existence of SCNECC and high-grade squamous intraepithelial lesion (HSIL) reflects the shared HPV-driven aetiology [7]. However, while HSIL tends to affect the epithelial layer, neuroendocrine tumours invade deeper tissues.

Neuroendocrine carcinomas typically present with irregular vaginal bleeding [3]. In one study, abnormal bleeding was preceded by post-coital bleeding (52.63%) and persistent discharge and vaginitis (36.84%). In 10.52%, irregular vaginal bleeding was the only symptom [1]. Cervical lesions may also be visible on examination, as demonstrated by this case. Essentially, symptoms specific to carcinoid symptoms are uncommon, since ectopic hormone secretion is rare [8].

Poorly differentiated cervical adenocarcinoma, SCC of the cervix and metastatic neuroendocrine carcinoma make up the main differential diagnoses of SCNECC [3]. Diagnosis may be aided by immunohistochemical markers, such as chromogranin A, synaptophysin, CD56 and neuron-specific enolase. Target next-generation gene sequencing technology may also detect genetic changes, which may shed light on the aetiology, while also contributing to advances in therapy. Such genetic changes may involve the MAPK, KRAS and p53/BRCA pathways [9]. Moreover, histological evaluation usually demonstrates round or spindle-shaped cells with hyperchromasia, lymphovascular invasion and necrosis [10].

SNECC is notorious for its poor prognosis, in view of its tendency for early lymph node involvement and distant metastasis. Also, such patients tend to present with advanced disease [1]. Consequently, the overall survival is around 3 years, with a 5-year survival rate of 34% [2]. This is dismal compared to the survival rate of squamous cell and adenocarcinoma of the cervix, which is known to be above 65% [2]. Poor prognostic indicators include bulky tumours, deep stromal invasion, lymph node involvement and progressive disease [9].

Controversy still lies in the management of SCNECC, and further research is still needed to inspire new treatment modalities which may improve clinical outcomes. Current evidence recommends a multimodal approach involving chemotherapy, radiotherapy, and surgery, namely radical hysterectomy, for disease in the early stage (stage IB1) [1, 9]. Interestingly, some studies demonstrated a poorer clinical outcome with direct radiotherapy compared to surgical management [11]. Thus, some literature favours radical surgery and chemotherapy for early disease (stage I-IIA). Primary radical hysterectomy may be considered in cases of tumors smaller than 2 cm in the absence of deep stromal or lymphovascular invasion. These patients can achieve favourable outcomes with postoperative adjuvant chemotherapy alone, potentially avoiding the need for adjuvant chemoradiation [9].

On the other hand, intermediate to advanced disease (stage IIB-IV) or cases of recurrence may be managed with chemotherapy and radiotherapy [12]. This is because of the similar clinical outcomes provided by chemotherapy and radiotherapy, compared to surgical management [9]. Essentially, in one study, a minimum of five cycles of chemoradiation with platinum and etoposide increased the five-year failure-free survival to 62.5% for stages IIB-IVB and cancer-specific survival to 75% for stages IIB-IVA. The 5-year cancer survival rate for stage IVB disease was 0% [13].

Nonetheless, future research is invaluable in paving the way for potential advances in targeted therapy, including the potential use of immunotherapy. This may include immune checkpoint inhibitors such as PD-L1, the levels of which tend to be elevated in HPV-as-

sociated disease [9].

Conclusion

This case report underlines the rare and aggressive nature of SCNECC, as well as its strong association with high-risk HPV serotypes. While clinical examination, histological evaluation, and imaging facilitate the diagnosis, the propensity for early lymph node involvement and distant metastasis as well as their tendency to present late contributes to their poor prognosis.

The scarcity of research on the management of SCNECC leaves many controversies on treatment modalities unsolved. However, a multimodal approach involving chemotherapy, radiotherapy and surgery is usually adopted. Promise lies in future research to explore the potential advantages that immunotherapy may hold in improving the outcomes of such a challenging condition.

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