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CASE REPORT

A CASE REPORT OF HPV NEGATIVE SMALL CELL NEUROENDOCRINE CARCINOMA AND SQUAMOUS CELL CARCINOMA OF THE CERVIX: A RARE BUT FATAL MIX

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ABSTRACT: Malignant neoplasms that show divergent differentiation, like squamous cell carcinoma (SCC) and small cell neuroendocrine carcinoma (SNEC), occur very rarely in the cervix. Neuroendocrine tumors of the female genital tract tend to occur in combination with other types of tumors although they have been also described to occur as solitary neoplasms. Here, we present a case of a 51-year-old woman with a one-month history of vaginal bleeding and one week history of persistent lower abdominal pain. On vaginal examination a large irregular fixed cylindrical mass in mid-vagina, extending to the cervix, was felt. A computerized tomographic scan showed a uterine mass with retroperitoneal and pelvic lymphadenopathy together with multiple bilateral lung metastases. Cytological analysis via a cervical pap smear reported a high-grade intraepithelial lesion and atypical glandular cells of undetermined significance. Histological analysis of the cervical biopsies showed a necrotic biphasic neoplasm. The morphological and immunohistochemical findings were those of a poorly differentiated carcinoma with squamous and high grade neuroendocrine (small cell) differentiation. Polymerase chain reaction analysis for Human Papilloma Virus (HPV) performed on shavings from the paraffin-embedded tissue showed no evidence of HPV DNA. The patient was planned to receive primary chemotherapy but passed away within 3 weeks of her diagnosis. In conclusion, tumors showing SNEC differentiation, together with rare cases of primary cervical SNEC exhibit a different disease profile when compared with pure cervical SCC, in that the former are highly aggressive and has a greater propensity for nodal and distant organ metastasis. These tumors are associated with a poor prognosis.

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Impact statement: This paper presents a case report of an HPV negative primary cervical SCC with divergent differentiation into SNEC. Such a combination is highly aggressive and has a greater propensity for nodal and distant organ metastasis, leading to a poor prognosis.

Key words: *small cell neuroendocrine cancer; squamous cell cancer; cervical cancer; prognosis; case report.*

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INTRODUCTION

Carcinomas of the cervix with divergent differentiation have been only sparsely reported and remain a very rare occurrence (1). This is particularly the case when considering the combination of squamous cell carcinoma (SCC) and small cell neuroendocrine carcinoma (SNEC) (2, 3). Neuroendocrine tumors of the female genital tract tend to occur in combination with other types of tumors although they have been also described to occur as solitary neoplasms. SNEC of the cervix exhibits a different disease profile when compared with SCC in that the former is much more aggressive and has a higher tendency for nodal and distant organ metastasis. These tumors are associated with a poor prognosis, with survival rates ranging from 17% to 67% depending on the stage at presentation. The clinical presentation of both SNEC and SCC include vaginal bleeding and abdominal pain. The treatment modalities available to treat these neoplasms include surgical interventions, chemotherapy and/or radiotherapy (4).

CASE PRESENTATION

A 51-year-old female, mother of two healthy children, presented to the Accident and Emergency Department with a one-month history of vaginal bleeding and one week history of persistent lower abdominal pain. She was obese and gave a history of hypertension, dyslipidemia, hypothyroidism and generalized anxiety disorder, all of which were controlled by medications. Although she was invited for cervical cancer screening, she never attended.

On abdominal examination, no masses were felt and no inguinofemoral lymphadenopathy was palpable. On vaginal examination a large irregular fixed mass in mid-vagina, extending to the cervix, was felt. The adnexae were not palpable. No family history of gynecological cancers was reported. Blood investigations including a full blood count, a renal profile and liver function tests were within normal range. Serum level of cancer-antigen 125 (CA125) were three times the upper limit of normal at 98.2 U/mL (range 0-30.2 U/ml) whilst the carcinoembryonic antigen (CEA) levels registered at more than twenty times the upper limit of normal at 52.7ng/mL (0-2.5). Similarly, cancer antigen 19.9 (CA19.9) was markedly elevated at 120 U/mL (0-33 U/ml) as was lactate dehydrogenase (LDH) (431 U/L;135-220 U/L). A computerized tomographic scan (CT) of the thorax, abdomen and pelvis was carried out which showed a uterine mass with retroperitoneal and pelvic lymphadenopathy together with multiple bilateral lung metastases (**Figure 1a** and **b**).

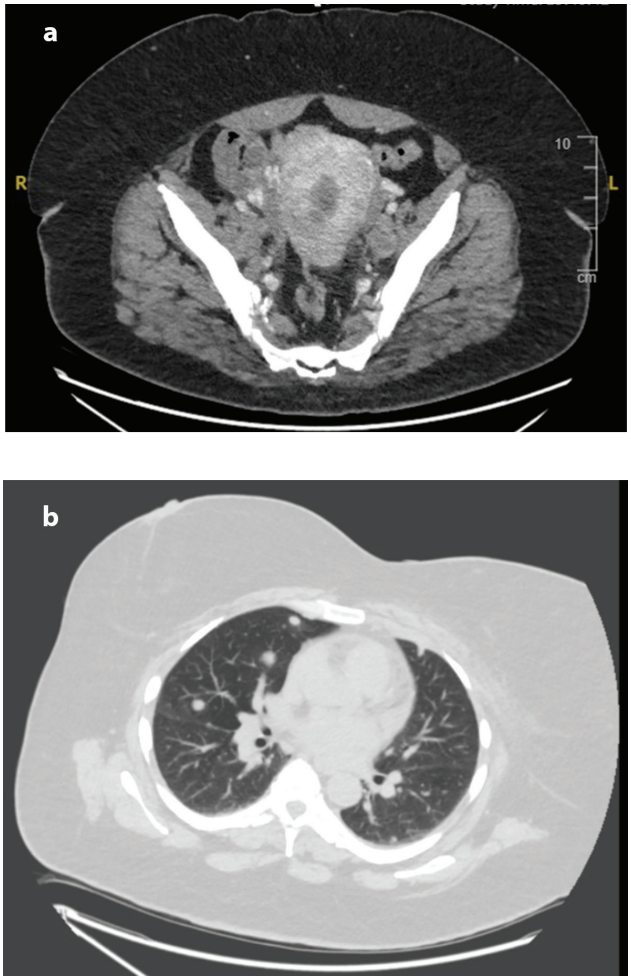

Figure 1. *(**a**) CT scan at the level of the pelvis showing the cervical mass (shown in green arrow) with pelvic lymphadenopathy (shown with yellow arrow); (**b**) at the thorax in lung window show metastatic deposits in the right lung marked with red arrows.*

A multiplanar magnetic resonance imaging (MRI) of the pelvis and cervix was carried out to better characterize the uterine tumor (**Figure 2**).

This showed a large, heterogenous mass replacing most of the anterior uterine wall and all the cervix. It measured 11 cm in maximum craniocaudal dimension and invaded the upper third of the vagina, filling the posterior fornix. Early parametrial invasion was noted at the 10 o'clock and 2 o'clock positions. The tumor showed heterogenous post-contrast enhancement and restricted diffusion. Additionally,

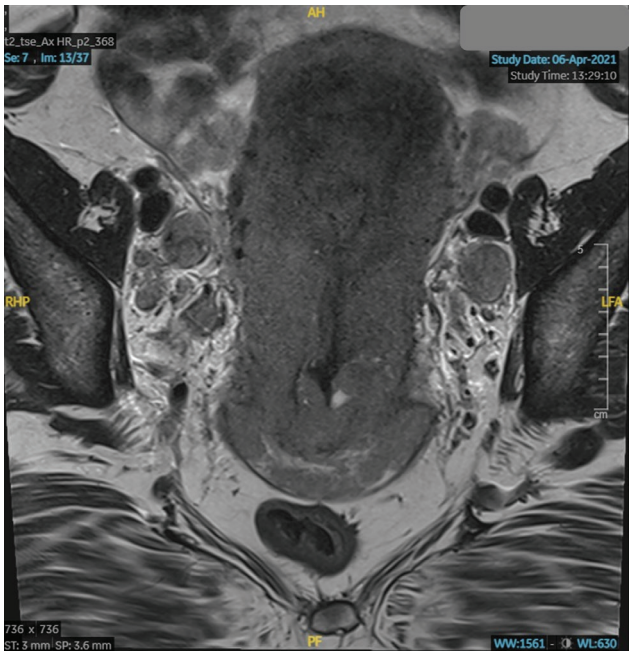

Figure 2. *MRI showing the cervical mass (shown with black arrows) with lymphadenopathy (shown with white arrows).*

there was extensive bilateral pelvic sidewall lymphadenopathy with the largest lymph node measuring more than 2 cm in maximum dimension. A 1.1 cm mesorectal lymph node was also noted and deemed to be suspicious for metastasis. On coronal sequences, there were retroperitoneal lymphadenopathy extending to the renal vessels. There was no evidence of obstructive uropathy and no evidence of upper abdominal organ metastasis. No ascites was present with no omental disease suspected. These findings staged the tumor to FIGO Stage IVB (5).

A cervical biopsy and endometrial pipelle biopsy were taken. Histological analysis of the cervical biopsies showed a necrotic biphasic neoplasm. The tumor was comprised of nests of relatively well-differentiated neoplastic squamous cells which abruptly transitioned to infiltrative sheets and clusters of undifferentiated tumor cells with scant cytoplasm, hyperchromatic nuclei and nuclear moulding (**Figure 3a**). The squamous component of the tumor showed expression of cytokeratin 5/6 (**Figure 3b**) and p63 (data not shown), while the more poorly differentiated component showed a neuroendocrine phenotype, expressing INSM1 (**Figure 3c**) and, more focally, synaptophysin (data not shown). The Ki67 proliferation fraction was 90% in the neuroendocrine component of the tumor (data not shown). The p16 expression was restricted to rare tumor cells (**Figure 3d**).

The morphological and immunohistochemical findings were those of a poorly differentiated carcinoma with squamous and high grade neuroendocrine (small cell) differentiation. The endometrial Pipelle biopsy showed fragments of tumor with an identical histomorphology to that described for the cervix. Polymerase chain reaction analysis for Human Papilloma Virus (HPV) performed on shavings from the paraffin-embedded tissue showed no evidence of HPV DNA.

After discussion during the multidisciplinary meeting, she was not deemed to be a surgical candidate and was offered primary chemotherapy. Regrettably she passed away within 3 weeks of her diagnosis and did not have the opportunity to benefit from chemotherapy. The cause of death was deemed to be due to the rapid progression of her metastatic disease. A post-mortem was not carried out for this patient.

DISCUSSION

This case adds to the very limited body of knowledge on patients with SCC exhibiting divergent SNEC differentiation. Cancer of the uterine cervix is the fourth most common malignancy in the female population worldwide and is also the fourth most common cause of cancer-associated mortality. Squamous cell carcinoma of the uterine cervix is the most common subtype of cervical cancer and carries a relatively favorable prognosis if detected early. Around 95% of cervical SCC are associated with the presence of one or more subtypes of human papilloma virus (HPV) (6). Combined tumor subtypes are rare, with adenosquamous carcinoma being the commonest tumor combination observed (3). Primary SNEC of the cervix is a vanishingly rare tumor, accounting for 1-2% of all cervical cancers, with cases of SCC exhibiting divergent differentiation being even rarer (1). The combination of SCC with SNEC has clinical repercussions both in the treatment modalities and prognostic outcomes.

Whilst the management of SCC according to the stage involves radical surgery, chemoradiotherapy with brachytherapy or combination chemotherapy, the presence of the SNEC component changes the strategy for treatment. Whilst there are no standardized modalities of treatment for SNEC given that these tumors are rare, most teams use a multimodal approach with chemo-radiotherapy often taking precedence on surgical excision. This

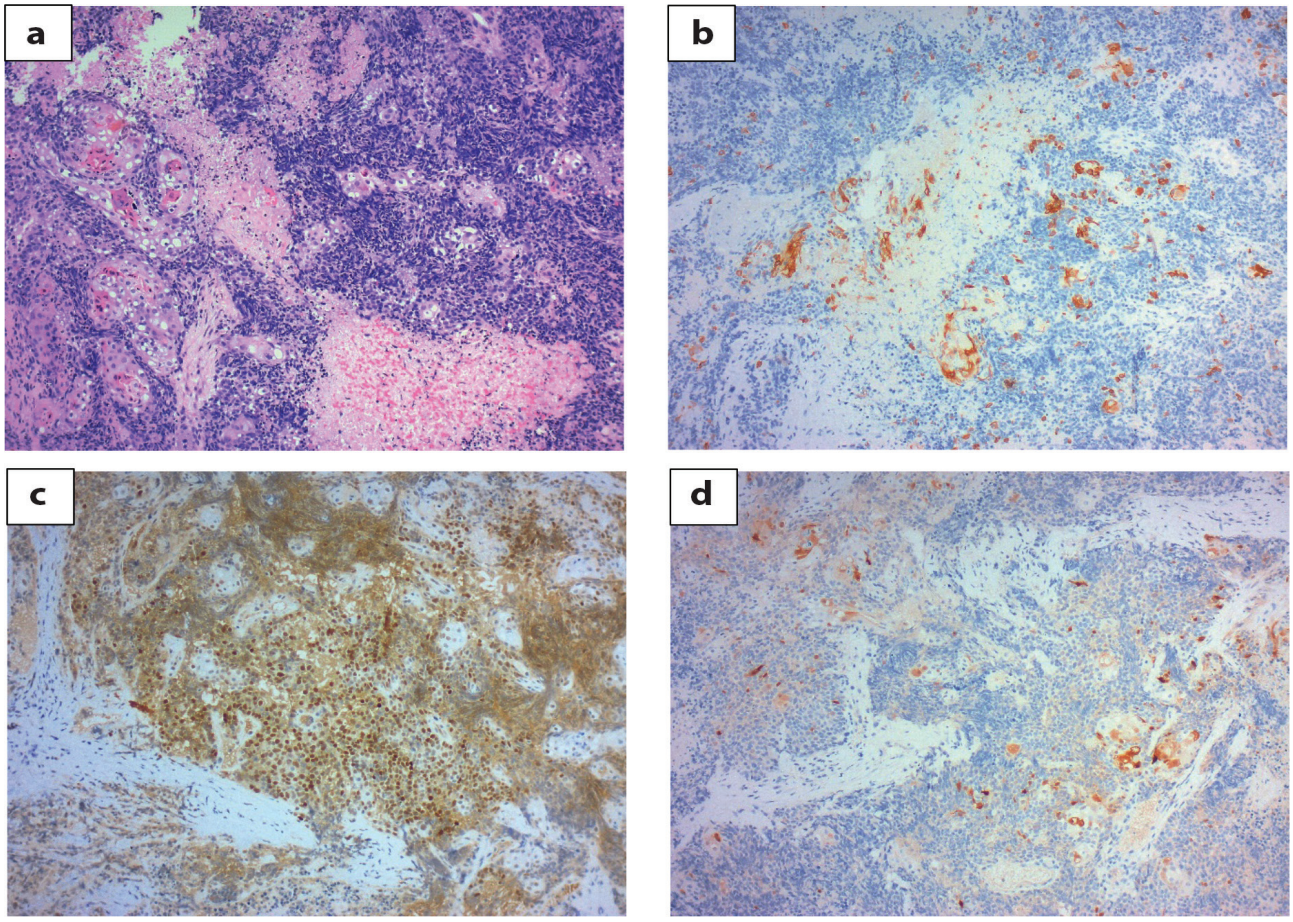

Figure 3. *(**a**) Histological analysis showing a distinctly biphasic neoplasm exhibiting both squamous differentiation (left), with nests of neoplastieosinophilic cells exhibiting central keratinization, and small cell neuroendocrine differentiation (right), with sheets of infiltrative, basaloid neoplastic cells. (H&E x 100). Immunohistochemistry showing expression of: (**b**) CK5/6 in the squamous component of the tumor, (**c**) INSM1 in the small cell neuroendocrine component and (**d**) focal p16 expression (IHC, x100).*

is usually a consequence of the advanced stage of the disease at presentation when these tumors are present. The combination of chemoradiotherapy has been shown to offer better results in the presence of SNEC. In terms of chemotherapy options, the regimen of choice typically mirrors that used for small cell neuroendocrine tumors of the lung and pancreas, which include a combination of etoposide and cisplatin or carboplatin (7). This was the modality of choice for the lady in the case we presented due to the advanced stage of disease at presentation. Unfortunately, this patient passed away before she could start treatment. Patients who either present at an early stage or who exhibit good response to chemo-radiotherapy may be candidates for radical resection. Novel treatment modalities that are more targeted and which address immune-checkpoint inhibitors are being developed in an attempt to improve outcomes particularly in patients with recurrent SNEC (8). Although these drugs are promising, there is a paucity of data to substantiate their routine use.

Both primary cervical SNEC and tumors showing SNEC differentiation carry an overall poor prognosis, with tumor behavior being primary dictated by the SNEC component. This is particularly the case given that patients are typically older, have evidence of lymph node spread, and present at an advanced stage. There is also some evidence to suggest that treatment with primary radiotherapy as opposed to multimodal treatment offers a worse prognosis. Overall, the mean survival of these patients is around 3 years. Patients who present with early stages have better prognosis (9) with a 5-year survival rate of 32% whilst patients who present late having the dismal outcome of 0% 5-year survival rate (10).

The relationship between HPV infection and SNEC is still controversial, unlike in SCC. Evidence has so far shown that the majority of patients with SNEC

have evidence of HPV infection (85%) particularly of subtypes 16 and 18 (11). The presence of HPV proliferation has also been shown to be linked to strong immunohistochemical expression of p16 (which is a cyclin-dependant kinase inhibitor). The latter together with Ki67 are considered sensitive markers for SNEC (12). Whilst Ki67 was abundant in the SNEC portion of this tumor, p16 was negative in this case. In addition, HPV PCR performed on this tumor also failed to reveal the presence of HPV. The link between SNEC and other viral pathogens such as Merkel cell polyomavirus were not proven in recent evaluations however larger studies are recommended to explore this hypothesis (13). Given this, it is possible that SCC showing SNEC differentiation represents a rare distinct tumor subtype whose pathogenesis is not HPV-driven.

CONCLUSIONS

Patients with a SCC of the uterine cervix exhibiting divergent SNEC differentiation present similar to other cervical tumors but have a poor prognostic outcome. Accurate histological assessment is imperative in order to counsel the patient appropriately and choose the right treatment modalities.

COMPLIANCE WITH ETHICAL STANDARDS

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Conflict of interests

The Authors have declared no conflicts of interests.

Availability of data and materials

The data presented in this study are available on request from the Corresponding Author.

Code availability

N/A.

Authors' contributions

AA and JCA: conceptualization; AA, CC and DP: writing; AA, CC, DP, RDF, AV, JDG, DV, NNM and JCA: writing-review and editing; JCA: funding acquisition. All Authors have read and agreed to the published version of the manuscript.

Ethical approval

Human studies and subjects

Informed consent has been obtained in writing from the patient's next of kin who is representing the patient, given that the patient is deceased. This case report contains clinical data from the patient's medical records.

Animal studies

N/A.

Publications ethics

Plagiarism

N/A.

Data falsification and fabrication

All the data correspond to the real.

REFERENCES

1. Varma KR, Dabbs DJ. Cervical carcinoma with divergent neuroendocrine and gastrointestinal differentiation. Int J Gynecol Pathol. 2018;37(5):488-91. doi: 10.1097/PGP.0000000000000438.
2. Vernekar M, Mandal A, Singh G, Banerjee D, Mandal R. Primary Synchronous Neuroendocrine, Adenocarcinoma and Squamous Cell Carcinoma of Cervix- A Case Report. J Surg Proce Case Rep. 2021;3:1-3. doi: 10.17303/jspcr.2021.3.102
3. Kaushal S, Mathur SR, Kumar S. Coexisting squamous cell carcinoma and high-grade neuroendocrine carcinoma, small cell type: A rare collision in cervix. BMJ Case Rep. 2018. doi: 10.1136/bcr-2017-223127.

4. Cohen JG, Kapp DS, Shin JY et al. Small cell carcinoma of the cervix: treatment and survival outcomes of 188 patients. Am J Obstet Gynecol. 2010;203(4):347.e1-347.e6. doi: 10.1016/j.ajog.2010.04.019.
5. Bhatla N, Berek JS, Cuello Fredes M, Denny LA, Grenman S, Karunaratne K, et al. Revised FIGO staging for carcinoma of the cervix uteri. Int J Gynecol Obstet. 2019;145(1):129-35. doi: 10.1002/ijgo.12749. Erratum in: Int J Gynaecol Obstet. 2019;147(2):279-80.
6. Li P, Ma J, Zhang X, Guo Y, Liu Y, Li X, et al. Cervical small cell carcinoma frequently presented in multiple high risk HPV infection and often associated with other type of epithelial tumors. Diagn Pathol. 2018;13(1):31-40. doi: 10.1186/s13000-018-0709-9.
7. Tempfer CB, Tischoff I, Dogan A, Hilal Z, Schultheis B, Kern P, et al. Neuroendocrine carcinoma of the cervix: A systematic review of the literature. BMC Cancer. 2018;18(1):530. doi: 10.1186/s12885-018-4447-x.
8. Paraghamian SE, Longoria TC, Eskander RN. Metastatic small cell neuroendocrine carcinoma of the cervix treated with the PD-1 inhibitor, nivolumab: A case report. Gynecol Oncol Res Prac. 2017;4:3. doi: 10.1186/s40661-017-0038-9.
9. Wang Y, Mei K, Xiang MF, Li JM, Xie RM. Clinicopathological characteristics and outcome of patients with small cell neuroendocrine carcinoma of the uterine cervix: case series and literature review. Eur J Gynaecol Oncol. 2013;34(4):307-10.
10. Chan JK, Loizzi V, Burger RA, Rutgers J, Monk BJ. Prognostic factors in neuroendocrine small cell cervical carcinoma. A multivariate analysis. Cancer. 2003;97(3):568-74. doi: 10.1002/cncr.11086.
11. Castle PE, Pierz A, Stoler, MH. A systematic review and meta-analysis on the attribution of human papillomavirus (HPV) in neuroendocrine cancers of the cervix. Gynecol Oncol 2018;148(2):422-9. doi: 10.1016/j.ygyno.2017.12.001.
12. Lu J, Li Y, Wang J. Small Cell (Neuroendocrine) Carcinoma of the Cervix: An Analysis for 19 Cases and Literature Review. Front Cell Infect Microbiol. 2022;12:916506. doi: 10.3389/fcimb.2022.916506.
13. Giordano G, D'Adda T, Pizzi S, Campanini N, Gambino G, Berretta R. Neuroendocrine small cell carcinoma of the cervix: A case report. Mol Clin Oncol. 2021;14(5):92. doi: 10.3892/mco.2021.2254.