Neuroendocrinology Letters Volume 44 No. 5 2023
ISSN: 0172-780X; ISSN-L: 0172-780X; Electronic/Online ISSN: 2354-4716
Web of Knowledge / Web of Science: Neuroendocrinol Lett
Pub Med / Medline: Neuro Endocrinol Lett

CASE REPORT

Small-cell neuroendocrine carcinoma of the cervix associated with adenocarcinoma in situ: A case report with analysis of molecular abnormalities

Vedran Madžarac[1], Diana Culej[1], Darija Mužinić[3], Gojko Zovko[1], Vanja Fenzl[1], Željko Duić[1,2]

1 Department of Obstetrics and Gynecology, University Hospital Merkur, Ivana Zajca 19, 10000 Zagreb, Croatia.
2 Medical school, University of Zagreb, Šalata 3b, 10000 Zagreb, Croatia.
3 Department of Pathology, University Hospital Merkur, Ivana Zajca 19, 10000 Zagreb, Croatia.

Correspondence to: Diana Culej
Huzjanova 6, Zagreb, Croatia
TEL/FAX: +385981931909, E-MAIL: diana.culej2010@gmail.com

Submitted: 2023-02-27 Accepted: 2023-06-28 Published online: 2023-07-16

Key words: **Small cell neuroendocrine carcinoma; adenocarcinoma in situ; human papillomavirus; molecular abnormalities; molecular diagnosis**

Neuroendocrinol Lett 2023; **44**(5):332–335 **PMID:** 37524322 NEL440523C02

Abstract

OBJECTIVE: We report a case of small-cell neuroendocrine carcinoma (SNEC) of uterine cervix associated with adenocarcinoma in situ (AIS), and we discuss prognosis, treatment benefit and goals of care.

CASE REPORT: A 36-year-old pluriparous woman presented with vaginal bleeding. Bimanual pelvic examination revealed a exophytic mass arising from the posterior lip of the cervix. A transvaginal ultrasound revealed endometrium thickness of 7mm and exophytic 39x19mm mass arising from the posterior lip of the cervix. Histopathological analysis of the tumorous lesion revealed a small-cell neuroendocrine carcinoma admixed with adenocarcinoma in situ. Differential immunohistochemistry of the small-cell neuroendocrine carcinoma component was CKAE1/AE3, CD 56, TTF -1 positive with diffuse expression of chromogranin and synaptophysin. HPV type 18 has been detected through PCR sequencing analysis. The next generation sequencing based on a 324-gene panel showed that tumor was microsatellite stable (MSS) with low mutational burden (TMB). Only missense mutations of FGF10, HSD3B1, NBN, PBRM1, RICTOR, SDHA were detected. Radical surgery was performed and the patient received adjuvant chemotherapy consisting of cisplatin/etoposide for six cycles. During 12 months of follow up the patient is free of disease.

CONCLUSION: Neuroendocrine tumour of uterine cervix is an extremely rare and aggressive cancer. Because of its low incidence there is still no standardized treatment approach based on controlled trials. Radical surgery and adjuvant or neoadjuvant chemotherapy is the mainstay of treatment.

INTRODUCTION

Small-cell neuroendocrine carcinoma of the cervix (SCNEC) is a rare entity of the female genital tract which accounts for less than 2 % of all invasive cervical cancers (Salvo *et al.* 2019). Association of small cell neuroendocrine carcinoma with other histological types has only occasionally been documented most often with adenocarcinoma or squamous cell carcinoma (Li & Zhu, 2013). The vast majority of SCNECs are etiologically

associated with high-risk human papillomavirus (HPV). While high-risk HPV is involved at an early stage of oncogenesis, other factors such as genetic and epigenetic alterations facilitate the progression of SCNECs (Xing *et al.* 2018). Small-cell neuroendocrine carcinomas are highly aggressive with early nodal and distant metastases, often resulting in a poor prognosis even when disease is clinically limited to the cervix. The management of SCNEC includes combination of surgery, chemotherapy and radiation therapy (Gardner *et al.* 2011). Despite extensive treatment this tumor carries a poor prognosis with mean overall survival of 40 months and 5-year overall survival rate of 34% (Xu *et al.* 2018). We present a case of small-cell neuroendocrine carcinoma of the cervix associated with adenocarcinoma in situ. Next generation sequencing of the SCNEC component was performed with the goal of identifying genetic alterations of this rare tumor.

CASE PRESENTATION

A 36-year-old woman gravida 3, para 2, was admitted to the Gynecology Department with a 14-day history of vaginal bleeding. The patient's medical history was unremarkable. Bimanual pelvic examination revealed a exophytic mass arising from the posterior lip of the cervix. The size of the uterus was physiological for age. A transvaginal ultrasound revealed endometrium thickness of 7mm and polypoid tissue at the cervical os meassuring 3.9x3.5cm. Biopsy of the tumorous lesion was taken and diagnosis of a small-cell neuroendocrine carcinoma (SCNEC) was made based on analysis of the sample. Magnetic resonance imaging revealed a cervical mass 3,5x3,1x1,7 cm. There was no extension of the lesion into the vagina, parametria, or adjacent organs including the bladder and rectum. Positron emission tomography–computed tomography (PET/CT) scanning of the chest, abdomen and pelvis revealed pathological glucose metabolism in uterine cervix, indicating active malignant tumor. There were no enlarged lymph nodes of thorax, abdomen or pelvis. The tumor was classified as clinical stage IB1 according to the guidelines of the International Federation of Gynecology and Obstetrics. Radical hysterectomy, bilateral salpingo-oophorectomy with pelvic and paraaortic lymphadenectomy was performed.

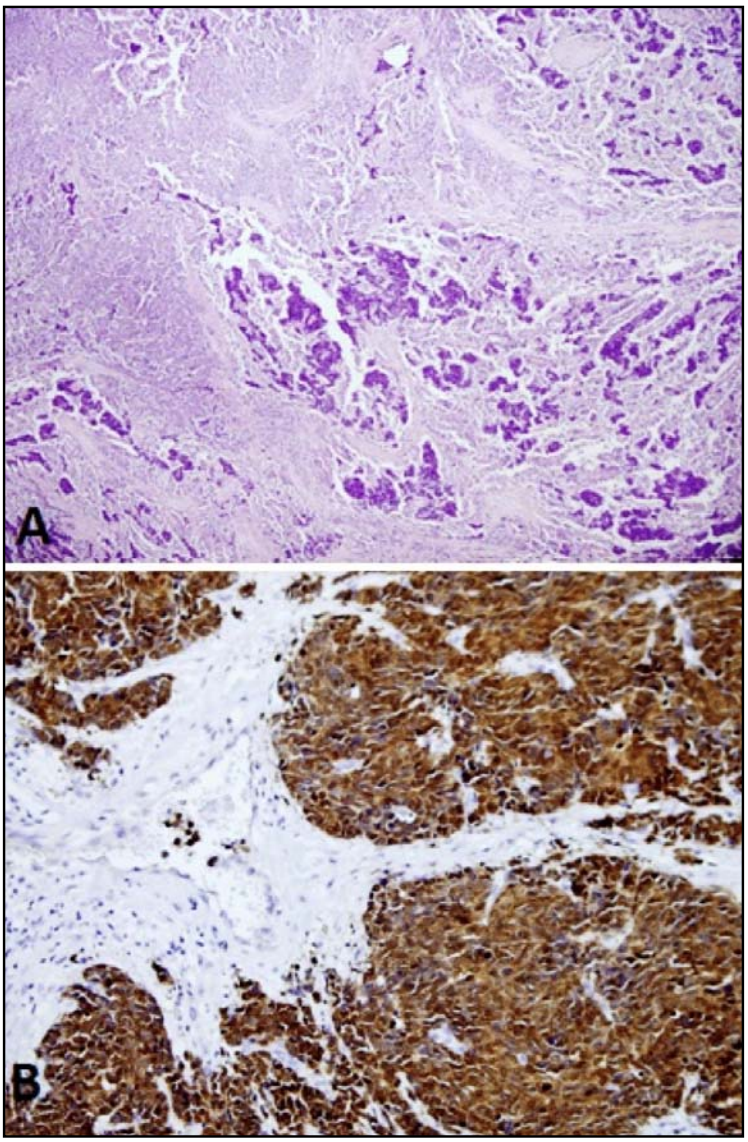

Fig. 1. A) Small cell neuroendocrine carcinoma. The scale bar indicates 500 µm (×40 magnification) (H&E).
B) Small cell neuroendocrine carcinoma. Immunohistochemical staining for p16 showing diffuse positive reactivity. The scale bar indicates 500 µm (×40 magnification).

Pathologic Findings

Gross examination of the resected uterus specimen demonstrated a polypoid lesion measuring 3,9 cm in diameter, present in the lower portion of the cervix. Histopathological analysis revealed diffuse proliferation of atypical small round cells forming irregular nests, characterized by hyperchromatic nuclei, high nuclear/cytoplasmic ratio and scant cytoplasm with „crushing" artifacts. Mitotic activity was high (more than 90 mitoses per mm^2 of the tumor tissue). The cells of this component were immunohistochemically CKAE1/AE3, CD56, thyroid transcription factor (TTF) 1 and p16 positive with diffuse expression of Chromogranin and Synaptophysin. No immunolabeling was disclosed for CD10, CD45, Bcl1.Expression of Ki-67 was observed in 90% of SCNEC cells. A diagnosis of small cell neuroendocrine

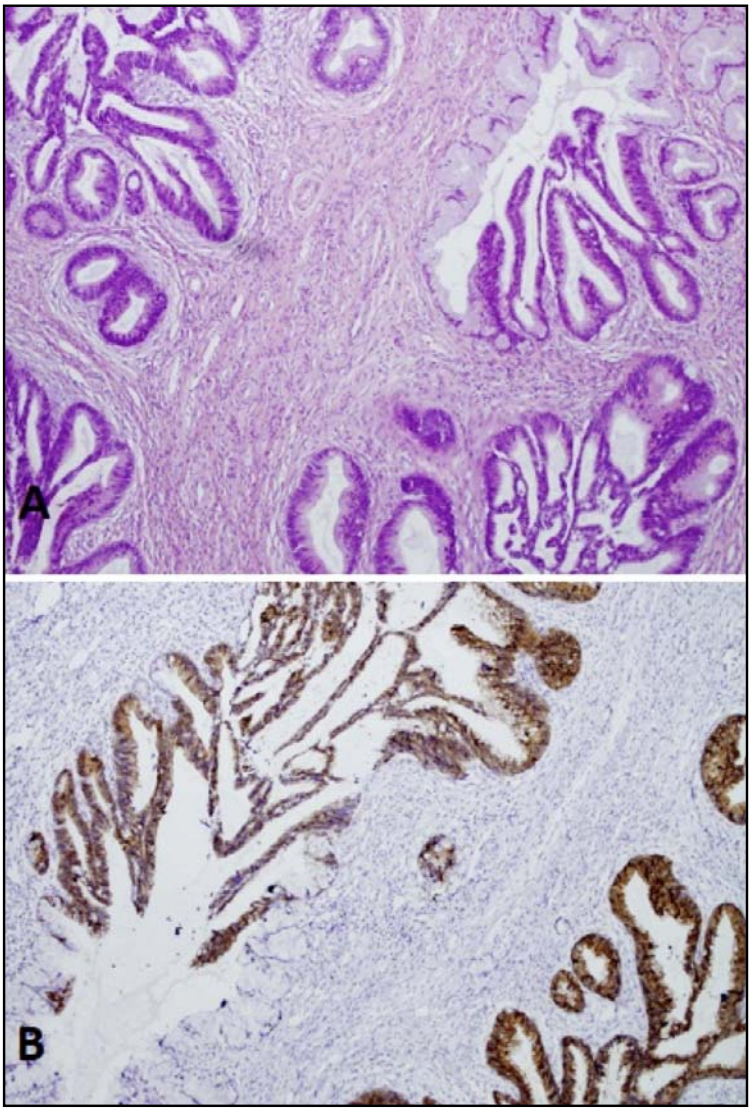

Fig. 2. A) Adenocarcinoma in situ in the hysterectomy specimen. The scale bar indicates 200 μm (×100 magnification) (H&E).
B) Adenocarcinoma in situ in the hysterectomy specimen. The cells of the adenocarcinoma in situ are immunoreactive for p16. The scale bar indicates 200 μm (×100 magnification). Normal mucinous endocervical glans are partially replaced by malignant darkened glands (black arrow).

carcinoma (SCNEC) was made (Figure 1). In addition, one of the slides demonstrated atypical glandular cells replacing the normal glandular mucosa of the endocervix while preserving its normal lobular architecture, with abrupt transition between the benign and atypical glandular cells. Diagnostic features included nuclear stratification, loss of the normal nuclear polarity, increased nuclear size, hyperchromasia and mitotic activity. The atypical glandular cells were also immunohistochemically positive for p16. The lesion was diagnosed as adenocarcinoma in situ (AIS) (Figure 2). No metastatic lesions were seen microscopically in the adnexa, vaginal cuff, or parametria, and the pelvic and para-aortic lymph nodes were negative.

Molecular abnormalities

The targeted next generation sequencing was performed using tumor DNA from SCNEC component extracted from formalin-fixed, paraffin-embedded (FFPE) tumor samples. Shotgun library construction and hybridization-based capture of all coding exons from 309 cancer-related genes, one promoter region, one non-coding (ncRNA), and select intronic regions from 34 commonly rearranged genes was performed. In total 324 genes were analysed. Missense mutations of FGF10, HSD3B1, NBN, PBRM1, RICTOR, SDHA were detected. The tumor was microsatellite stable (MSS) and tumor mutational burden (TMB) was low (0 muts/Mb). No structural alterations, including large gene deletion, duplication, inversion, or translocation were detected.

HPV studies

Human papillomavirus typing by polymerase chain reaction was HPV-18 positive for both SCNEC and AIS component.

Follow up

The patient received adjuvant chemotherapy consisting of cisplatin 60 mg/m^2 on day one and etoposide 100 mg/m^2 on days 1-3 every 3 weeks for six cycles. At 12 months follow-up the patient was free of disease.

DISCUSSION

Neuroendocrine tumour of uterine cervix is an extremely rare and aggressive cancer. Because of its low incidence there is still no standardized treatment approach based on controlled trials. Radical surgery and adjuvant or neoadjuvant chemotherapy is the mainstay of treatment for early stage neuroendocrine carcinomas. Currently there is no standard chemotherapy regimen for NECC, but cisplatin/carboplatin and etoposide is most commonly used treatment scheme. Patients with locally advanced disease are treated with combined radiochemotherapy and chemotherapy (Gardner *et al.* 2011). In case of recurrent disease in some centers triplet regimen including topotecan, paclitaxel, and bevacizumab has been used (Tempfer *et al.* 2018). Recently several studies evaluated genetical abnormalities of NECC trying to find a possible novel strategy in treatment of these tumors. This approach led to utilisation of altered molecular pathways which presumably can be targeted in clinical trials. Most commonly observed

mutation in neuroendocrine tumors is TP53, however data regarding its occurrence are inconsistent (Ishida *et al.* 2004, Wistuba *et al.* 1999). Neuroendocrine tumors of uterine cervix are commonly associated with high risk HPV infection, therefore in some cases of NECC loss of p53 function can be mediated via HPV encoded gene product E6. Although HPV 18 was detected, TP53 mutation was not observed in our case. PIK3CA is another commonly detected mutation in SCNEC which plays critical role in HPV induced carcinogenesis by mediating of growth and differentiation of HPV-immortalized cells (Henken *et al.* 2011). Additionally KRAS mutation which are commonly present in endocervical adenocarcinoma were also observed in SCNEC tumors (Lyons *et al.* 2014). However, neither of mentioned alterations has been detected in our case. Detection of missense mutations of FGF10, HSD3B1, NBN, PBRM1, RICTOR, SDHA demonstrates that some cases of small-cell neuroendocrine tumors have unique set of gene alterations and warrants further investigation of molecular abnormalities in a larger cohort. Cervical small-cell neuroendocrine carcinomas usually occur in uterine cervix in pure form, although in rare cases these tumors have adenocarcinoma or squamous cell carcinoma component (Lyons *et al.* 2014, Pao *et al.* 1991). Mixed forms of tumors can be a result of a rare event of development of two synchronous carcinoma. However, it seems that more frequently mixt tumors develop as a result of divergent differentiation of clonal cell driven by high risk HPV infection. Connection between cervical SCNEC and high-risk HPV, especially HPV-18 is well established (Pao *et al.* 1991). Nishiumi *et al.* found that p16(INK4a) which has been recognized as surrogate marker of high risk HPV infection was diffusely expressed in both AIS and SCNEC components (Nishiumi *et al.* 2018). Alphandery *et al.* detected the presence of HR-HPV DNA 18 in both endocervical adenocarcinoma and small-cell neuroendocrine carcinoma arguing that the two components of the tumor shared the same cell origin (Alphandery *et al.* 2007). Furthemore, Ishida *et al.* found loss of heterozygosity (LOH) at the same locus 17q22 in both SCNEC and adenocarcinomatous components in one tumor (Ishida *et al.* 2004). More information about origin of each component could be available if additional molecular analysis of adenocarcinoma in situ was done. Unfortunately due to small volume of AIS component only molecular abnormalities of SCNEC tumor could be performed in this case. More significant utilisation of a targeted next-generation gene sequencing technology can be used to broader our insight into genetic alterations of these rare tumors. Accordingly, development of successful targeted therapies could be possible as well as their implementation in a more individualized management strategies.

DECLARATION OF COMPETING INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this paper.

ACKNOWLEDGEMENT

None.

ETHICAL COMMITTEE APPROVAL

All necessary ethical considerentions and guidelines were adhered to regarding the publication of this paper.

REFERENCES

1 Alphandery C, Dagrada G, Frattini M, Perrone F, Pilotti S (2007). Neuroendocrine small cell carcinoma of the cervix associated with endocervical adenocarcinoma: a case report. Acta Cytol. **51**(4): 589–93.
2 Gardner GJ, Reidy-Lagunes D, Gehrig PA (2011). Neuroendocrine tumors of the gynecologic tract: A Society of Gynecologic Oncology (SGO) clinical document. Gynecol Oncol. **122**(1): 190–8.
3 Henken FE, Banerjee NS, Snijders PJ, Meijer CJ, De-Castro Arce J, Rösl F, et al. (2011). PIK3CA-mediated PI3-kinase signalling is essential for HPV-induced transformation in vitro. Mol Cancer. **10**: 71.
4 Ishida GM, Kato N, Hayasaka T, Saito M, Kobayashi H, Katayama Y, et al. (2004). Small cell neuroendocrine carcinomas of the uterine cervix: a histological, immunohistochemical, and molecular genetic study. Int J Gynecol Pathol. **23**(4): 366–72.
5 Li S, Zhu H (2013). Twelve cases of neuroendocrine carcinomas of the uterine cervix: cytology, histopathology and discussion of their histogenesis. Acta Cytol. **57**(1): 54–60.
6 Lyons YA, Frumovitz M, Soliman PT (2014). Response to MEK inhibitor in small cell neuroendocrine carcinoma of the cervix with a KRAS mutation. Gynecol Oncol Rep. **10**: 28–9.
7 Nishiumi Y, Nishimura T, Kashu I, Aoki T, Itoh R, Tsuta K, et al. (2018). Adenocarcinoma in situ admixed with small cell neuroendocrine carcinoma of the cervix: A case report with cytological features. Diagn Cytopathol. **46**(9): 752–755.
8 Pao CC, Lin CY, Chang YL, Tseng CJ, Hsueh S (1991). Human papillomaviruses and small cell carcinoma of the uterine cervix. Gynecol Oncol. **43**(3): 206–10.
9 Salvo G, Gonzalez Martin A, Gonzales NR, Frumovitz M (2019). Updates and management algorithm for neuroendocrine tumors of the uterine cervix. Int J Gynecol Cancer. **29**(6): 986–995.
10 Tempfer CB, Tischoff I, Dogan A, Hilal Z, Schultheis B, Kern P, et al. (2018). Neuroendocrine carcinoma of the cervix: a systematic review of the literature. BMC Cancer. **18**(1): 530.
11 Wistuba II, Thomas B, Behrens C, Onuki N, Lindberg G, Alberes-Saavedra J. (1999). Molecular abnormalities associated with endocrine tumors of the uterine cervix. Gynecol Oncol. **72**(1): 3–9.
12 Xing D, Zheng G, Schoolmeester JK, Li Z, Pallavajjala A, Haley L, et al. (2018). Next-generation Sequencing Reveals Recurrent Somatic Mutations in Small Cell Neuroendocrine Carcinoma of the Uterine Cervix. Am J Surg Pathol. **42**(6): 750–760.
13 Xu F, Ma J, Yi H, Hu H, Fan L, Wu P, et al. (2018). Clinicopathological Aspects of Small Cell Neuroendocrine Carcinoma of the Uterine Cervix: a Multicenter Retrospective Study and Meta-Analysis. Cell Physiol Biochem. **50**(3): 1113–1122.