

Case Report

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# Combined Large-Cell Neuroendocrine and Squamous Cell Carcinoma of the Uterine Cervix with a Personal History of the Primary Breast Duct Carcinoma in situ: A Clinicopathological Characteristic and Outcome

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## Keywords

Large-cell neuroendocrine carcinoma-SCC · Cervical cancer · Prognosis

## Abstract

Squamous cell carcinoma admixed with large-cell neuroendocrine carcinoma of the uterine cervix is an extremely rare malignancy with a poor prognosis. We report a 50-year-old woman with mixed squamous cell carcinoma and large-cell neuroendocrine carcinoma of the uterine cervix with an individual history of early-stage breast cancer. She was diagnosed preoperatively with cervical cancer stage FIGO 1B2. However, during surgery, a lesion was found in Douglas's peritoneum. The histopathological result of surgical specimens was mixed squamous cell carcinoma and large-cell neuroendocrine carcinoma. Then, she received concurrent chemoradiotherapy. Currently, after 3 months of treatment, she has not developed recurrent lesions.

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## Introduction

Squamous cell carcinoma admixed with large-cell neuroendocrine carcinoma (LCNEC) of the uterine cervix is an extremely rare malignancy with a poor prognosis. In the literature, there are not any reported cases. Primary gynecologic neuroendocrine neoplasms (NENs) constitute under 2% of female reproductive tumors [1]. Most of them present a pure form, and only 4% of this type of tumor is associated with adenocarcinoma [2, 3], much less common with squamous cell carcinoma. Overall, NENs of the gynecologic tract are uncommon and aggressive, with high recurrence rates and dismal prognosis, making their treatment challenging [4]. In a study by Crane et al. [5], the origin of these neoplasms in the cervix is highest, at 54%. In the fifth edition of the WHO terminology of Gynecological NENs, cervical NENs are classified into cervical neuroendocrine tumors (NETs: carcinoid/grade 1 and atypical carcinoid/grade 2) and high-grade cervical neuroendocrine carcinomas (NECs: small cell and/or large-cell type, grade 3) based on Ki-67 and the mitotic index. High-grade NECs are expressed with a high Ki67 index (more than 20%) and >20/10 HPF mitotic indices and include small- and large-cell NECs [1]. Large-cell NECs account for only about 12% of cervical NENs [4]. High-grade NEC of large cell has the diffuse organoid, trabecular or cord-like patterns. Sometimes, it can be difficult to distinguish between poorly differentiated squamous and adenocarcinomas. These tumors are aggressive and have a similar outcome to small-cell carcinoma [6]. NECs may also coexist with adenocarcinoma or squamous cell carcinoma, and the clinical behavior of such cases is determined by the neuroendocrine component [7]. In the cervical combined histopathological types, squamous cell carcinoma is a much less common non-neuroendocrine component, compared to adenocarcinoma [8]. Here, we present the clinicopathological entity and outcome of the first case in Vietnam.

## Case Presentation

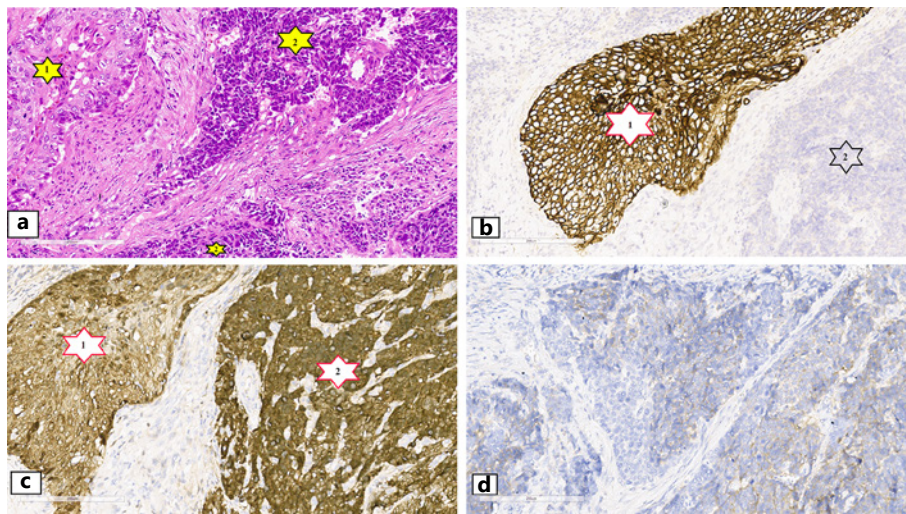
### *Clinical Case*

A 50-year-old premenopausal Vietnamese woman had 20 days menorrhagia. She had a personal cancer history. In September 2020, she was diagnosed with left breast cancer pTisN0M0 and experienced a nipple-sparing mastectomy with grade 2 intraductal carcinoma, ER(++), 60%, PR(++), 40%, negative HER2, and Ki67(+) 10%. Currently, she is taking tamoxifen. For the next 14 months, in November 2021, she went to a local hospital to found a tumor in her cervix, afterward; she was taken a punch biopsy. The histopathological result was invasive squamous cell carcinoma of the cervix, so she was referred to our hospital.

Tumor markers of SCC and CA125 antigens were at 0.9 ng/mL and 12 U/mL, respectively. Pelvic examination revealed a mass of 2 × 3 cm in size, which is localized in the cervix, without invasion of the vagina and parameter. The tumor was assessed as stage IB2 according to the International Federation of Obstetrics and Gynecology (FIGO) classification system. Pelvic magnetic resonance imaging showed a cervical mass that was hyperintense on T2-weighted, localized, and without extension into the vagina, and bilateral broad ligaments. Positron emission computed tomography (CT) showed no local or distant metastases. She was operated on by a bilateral pelvic lymphadenectomy, para-aortic lymphadenectomy, and bilateral salpingo-oophorectomy as initial treatment. However, during the operation, a Douglas peritoneal lesion measuring 0.5 cm was discovered, and the surgeon proceeded to remove it.

### *Pathological Features*

Histology of cervical surgical specimens showed mixed squamous cells and large-cell neuroendocrine cells with a more predominant malignant squamous epithelial component



**Fig. 1.** **a** Microscopic picture showed the foci of squamous cell carcinoma (the first star), broad trabecular, and small nest or sheets of large-cell neuroendocrine components (the second stars) (HE stains.  $\times 20$ ). Photomicrographs indicated the strong positive immunohistochemical markers. **b** Cytokeratin 7 is positive for squamous cell carcinoma (the first star) and negative for neuroendocrine component (the second star). **c** P16 is positive for both cancer components (the first and second stars). **d** Synaptophysin is only positive for neuroendocrine component (IHC stain.  $\times 20$ ).

(Fig. 1a). The large-cell neuroendocrine component invaded deeper than malignant squamous carcinoma, but the less third of cervical thickness. The tumor tissue consists of two distinct components: squamous cell carcinoma and LCNEC. Squamous cell carcinoma predominates with groups of epithelial cells, which have large, irregular nuclei, multiple mitotic nuclei, and abundant eosinophilic cytoplasm. Neuroendocrine carcinoma accounts for a lesser percentage, which is a diffuse, with large, strongly hyperchromatic, enlarged nuclei. The histopathology of peritoneal Douglas mass was metastatic LCNEC, without squamous cell carcinoma. The tumor showed lymph vascular invasion and no parametric invasion. No metastatic cancer was found in the twenty-three examined lymph nodes, including bilateral iliac and intra-abdominal aorta lymph nodes.

Immunohistochemically, tumor cells were immunoreactive to CK7, p16, and synaptophysin (Fig. 1b–d). The cancer cells were negative for CD56, chromogranin, CD57, and NSE.

She was eventually diagnosed with cervical cancer, stage FIGO IVa according to the 8th AJCC, due to the Douglas peritoneal metastasis, mixed squamous cell and LCNEC. However, no cancerous lesions were found in postoperative PET/CT scans in any parts of the body.

#### *Treatment and Outcomes*

After 30 days of the radical surgery, she received concurrent chemoradiotherapy with 50-Gy pelvic radiotherapy and EP regimen (cisplatin 50 mg/m<sup>2</sup> on day 1 every 3 weeks and etoposide 100 mg/m<sup>2</sup> on days 1–3 every 3 weeks). Overall reevaluation was conducted after 1 month of the end of treatment, and the results showed no lesions and tumor markers were within the normal level. Hence, she was discharged from the hospital and continuously received aromatase inhibitor endocrine therapy for breast cancer. Currently, after finishing treatment for 3 months, she has not developed any recurrent lesions.

## Discussion

Squamous cell carcinoma admixed with neuroendocrine carcinoma of the uterine cervix is a very rare malignancy with a poor prognosis and there are a limited number of cases in the literature. Gynecological tract NENs are rare, aggressive by endocrine cells derived from the neuroectoderm, neural crest, and endoderm. This disease was discovered in the late 19th century by Langhans and Lubarsch [9]. According to the 2020 WHO classification of female genital tumors, LCNECs have a characteristic neuroendocrine morphology with large cells and are positive for neuroendocrine-specific immunohistochemical markers [8]. Neuroendocrine biomarkers, including synaptophysin, chromogranin A, CD56, CD57, neuron-specific enolase, synaptic vesicle protein 2, and protein gene product 9.5, are used to identify NENs [4]. Also, the term for cervical NETs was presented in 1997 and is similar to the terminology used for pulmonary NETs [10].

Sometimes, the new cancer is in the same organ or area of the body as the first cancer. The follow-up time since the longer patients are followed up after a primary cancer diagnosis, the higher the likelihood that they may develop a second malignancy and importantly also the patient population studied [11]. The number of patients with second malignant neoplasms is growing, with new second malignant neoplasms now representing about one in six of all cancers reported to the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program [11]. Our patient had got 2nd cancer – cervical cancer after 14 months of breast cancer treatment. Immunohistochemical staining showed that tumor cells were positive for p16. This result suggests that the patient may have been infected with HPV. Today, the association between certain histopathological types of breast cancer and HPV is being investigated [12]. Unfortunately, we no longer have breast cancer samples to analyze the association with HPV status. The information of this case could be data for future studies that focus on the association between these two cancers.

In squamous cell carcinoma admixed with neuroendocrine carcinoma of the uterine cervix, the poor prognosis is mostly related to the behavior of the neuroendocrine component. The malignant neuroendocrine component is often more aggressive, and distant metastases occur more frequently and earlier compared with other cancer components. In this case, the Douglas peritoneal metastasis was merely the neuroendocrine component and not the squamous cell carcinoma. Therefore, histologically, one report showed that LCNECs could be of a mixed type, coexisting with small-cell neuroendocrine carcinoma, adenocarcinoma, or squamous cell carcinoma, in which cases, this study highlights the importance of biopsies of sufficiently large size to ensure accurate diagnosis [13]. During histological examination with cervical biopsy, small-cell neuroendocrine carcinoma diagnoses may be intervened with the other malignancies, for example, nonkeratinized squamous cell carcinoma because it contains a neuroendocrine component in a limited number of nested patterns [2]. Histologically, in squamous cell carcinoma, the nuclei are hyperchromatic with coarsely granular and irregularly distributed chromatin. Nuclear molding is usually absent in squamous cell carcinoma. Especially, nuclear molding should be considered the typical morphological features of small-cell neuroendocrine carcinoma [14]. This patient's initial cervical biopsy presented only the squamous cell carcinoma component. This may be due to the small biopsy piece, which is not representative of the entire tumor. The differential diagnosis is very important because the aggressive behavior of the tumor with malignant neuroendocrine component urges more aggressive treatment than other usual carcinomas of the cervix. As it is an uncommon disease, there are limited data on the most common sites of cervical NET metastasis. According to a report by Sato et al. [15] based on an analysis of 6 LCNCC patients, LCNCCs exhibit aggressive behavior, similar to pulmonary NETs, and often metastasize to lymph nodes, lungs, liver, bones, and brains. In this patient, the preoperative checkup did not show any metastases; however, during her operation, a 5-mm metastatic nodule was found in the Douglas peritoneum. Looking closely at the preoperative magnetic resonance imaging, we found a small lesion at this site, but its size is very small and resembles the structure of a benign lymph node.

When NEC coexists with adenocarcinoma or squamous cell carcinoma, the clinical behavior of these cases is determined by the neuroendocrine component. Therefore, the regimen given is similar to NEC alone. Although there are no optimal treatment guidelines for this subgroup, surgery is recommended and followed by adjuvant therapy in the early stage [4]. Our patient, with an initial diagnosis of FIGO IB2, underwent surgery. Although a peritoneal metastatic nodule was later detected, the surgery was considered to be a radical treatment when the 18FDG-PET/CT scan showed no more lesions. Then, concurrent chemoradiotherapy with EP regimen was initiated. 2 cycles of chemotherapy was administered with radiation therapy and 2 cycles after the end of radiotherapy. Currently, 3 months after the end of treatment, she has not developed any recurrent lesions.

## Conclusions

Squamous cell carcinoma admixed with large-cell neuroendocrine carcinoma of the uterine cervix is an extremely rare aggressive tumor, with a poor prognosis belonging to the neuroendocrine component as compared to similar stages of squamous cell carcinoma. Due to the rarity, it is challenging to diagnose and determine the most appropriate therapy protocol. The present case suggests that it is crucial for pathologists and/or oncologists to recognize this rare entity.

## Statement of Ethics

Ethical approval is not required for this study in accordance with local guidelines. The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published, and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

## Conflict of Interest Statement

There are no conflicts of interest.

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## Author Contributions

Duc Thanh Le should be considered the primary author. He participated directly in diagnosis, treatment, and follow-up of the patients; performed literature review; and assisted in drafting of the components of the case report and in formatting the presented material. Kien Hung Do and Tu Anh Do took part in the diagnostic and treatment consultant and assisted in

literature review. Hoai Thu Thi Bui performed follow-up of the patient, review of patient's chart, literature review, and assisted in drafting of the components of the case report. Chu Van Nguyen performed the diagnostic consultant of the HE stains and immunohistochemical staining, the literature review, took illustrated figures, assisted in drafting of the components of the case report, and assisted in formatting the presented material.

### Data Availability Statement

All data analyzed during this case report are included in this article. Further inquiries can be directed to the corresponding author.

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