

## Case Series

## Neuroendocrine Cervical Carcinoma

## Karsinoma Serviks Neuroendokrin

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## Abstract

**Objective:** To present a case series of neuroendocrine cervical carcinoma, a rare malignancy of the cervix characterized by varying stages, treatment approaches, and outcomes. The article provides a comprehensive review of diagnostic strategies, treatment modalities, and prognostic considerations for managing neuroendocrine cervical carcinoma.

**Methods:** Case report

**Cases:** Three cases of neuroendocrine cervical carcinoma are reported. The first case involves a 40-year-old woman, para 2, diagnosed with stage IIIB neuroendocrine cervical carcinoma, who opted for palliative care. The second case features a 54-year-old woman, para 5, with stage IIB neuroendocrine cervical carcinoma, treated with radiotherapy and achieving a disease-free period of 4 months. The third case showcases a 36-year-old woman, para 2, diagnosed with stage IB1 neuroendocrine cervical carcinoma. She underwent a radical abdominal hysterectomy with pelvic lymphadenectomy and external pelvic radiotherapy, achieving disease control without recurrence for 15 years.

**Conclusion:** Distinguishing neuroendocrine cervical carcinoma from other cervical malignancies is crucial, with immunohistochemistry (IHC) offering valuable diagnostic insights. Tailored treatment plans are essential for managing these malignancies, with a preference for multimodality approaches to enhance overall outcomes.

**Keywords:** cervical carcinoma, multimodality treatment, neuroendocrine cervical carcinoma.

## Abstrak

**Tujuan:** Melaporkan serangkaian kasus neuroendocrine cervical carcinoma, salah satu jenis keganasan langka pada area serviks dengan stadium, tata laksana, dan hasil yang berbeda. Dalam artikel ini juga terdapat ulasan mengenai prosedur diagnosis, manajemen, dan prognosis dari neuroendocrine cervical carcinoma.

**Metode:** Laporan kasus

**Kasus:** Artikel ini melaporkan tiga kasus. Pertama perempuan 40 tahun riwayat partus dua kali dengan karsinoma serviks neuroendokrin stadium IIIB dan hanya memilih perawatan paliatif. Kasus kedua, perempuan 54 tahun, riwayat partus lima kali dengan karsinoma serviks neuroendokrin stadium IIB. Pada pasien dilakukan terapi radiasi dan didapatkan kondisi bebas penyakit selama 4 bulan. Terakhir, pasien perempuan 36 tahun riwayat partus dua kali dengan karsinoma serviks neuroendokrin stadium IB1. Dilakukan histerektomi radikal dan limfadenektomi kelenjar limfe pelvis serta terapi radiasi. Kondisi pasien terkontrol dan tidak terdapat kekambuhan setelah 15 tahun.

**Kesimpulan:** Karsinoma serviks dengan jenis neuroendokrin harus dibedakan dengan keganasan lain pada daerah serviks. Uji imunohistokimia dapat digunakan untuk membedakan hal tersebut. Selain itu, penyusunan rencana tatalaksana untuk mengatasi keganasan pada serviks juga harus menjadi perhatian penting bagi klinisi. Direkomendasikan untuk menerapkan tata laksana multimodal untuk mencapai hasil terapi yang optimal.

**Kata kunci:** karsinoma serviks, karsinoma serviks neuroendokrin, tata laksana multimodal.

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## INTRODUCTION

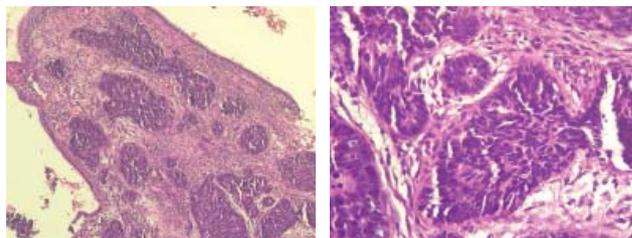
Neuroendocrine neoplasms (NENs) constitute an infrequent and heterogeneous category of cancers that can manifest in various locations throughout the body, originating from diffuse neuroendocrine system cells<sup>1</sup>. While NENs are most frequently encountered in the gastrointestinal system, pancreas, and lungs within humans, they can also manifest in diverse organs, including the female genital tract<sup>2</sup>. Referred to as Neuroendocrine Carcinoma of the Cervix (NECC) or simply NECC, this malignancy constitutes approximately 1% of all cervical cancer diagnoses in the United States. Despite its rarity, NECC presents as an aggressively histologic subtype within an otherwise predominantly benign context<sup>3</sup>. The rarity of this cancer type imparts challenges and complexities to NECC management. This is exacerbated by the fact that the majority of research concerning neuroendocrine tumor treatment has been conducted on patients with tumors affecting organs other than the cervix, mainly focusing on the lungs and pancreas.

Diverging from characteristics of squamous cell carcinoma or adenocarcinoma of the cervix, NECC exhibits distinct attributes. Notably, NECC tends to infiltrate the lymph-vascular space and extend to local lymph node basins at the time of diagnosis<sup>4</sup>. Furthermore, NECC displays considerably inferior 5-year overall survival rates approximately 30% contrasted with rates exceeding 65% observed in squamous cell carcinoma and adenocarcinoma of the cervix. The incidence of both local and distant relapses is also notably elevated within NECC cases<sup>3</sup>.

### Case I

A 40-year-old woman, para 2, was admitted with the chief complaint of abnormal uterine bleeding. The patient had a history of post-menstrual spotting. During the gynecological examination, a mass larger than 4 cm was detected in the cervix, extending to the pelvic sidewalls (classified as Stage IIIB in the FIGO staging system). The Papanicolaou smear revealed a high-grade malignant tumor exhibiting lymphovascular invasion, and it was diagnosed as poorly differentiated squamous cervical cancer, grade 3. A tissue biopsy was performed, and Immunohistochemistry (IHC) testing confirmed the presence of neuroendocrine carcinoma.

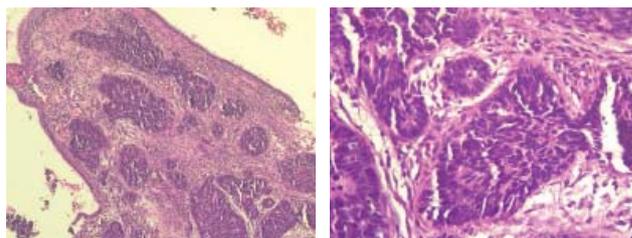
The patient subsequently received palliative treatment.



**Figure 1.** Case I Under microscopy, the neoplasm show a solid structure with round nuclei, forming a rosette like structure and numerous mitoses.

### Case II

A 54-year-old woman, para 5, was admitted to the hospital due to abnormal uterine bleeding. A mass larger than 4 cm was identified in the cervix during the gynecological examination. The mass extended to the upper two-thirds of the vagina with parametrial invasion, placing it at Stage IIB according to the FIGO Staging system. Tissue samples were obtained for Papanicolaou smear and Immunohistochemistry (IHC) testing. The Papanicolaou smear revealed the presence of malignant cells, while the results of the Immunohistochemistry (IHC) test indicated neuroendocrine carcinoma. Subsequently, the patient underwent radiotherapy treatment. As of now, the disease is well controlled, and there has been no recurrence within a four-month period.



**Figure 2.** Case II Under microscopy, the neoplasm show a solid structure with evident round or ovoid nuclei, forming a rosette like structure and numerous mitoses.

### Case III

A 36-year-old woman, para 2, was admitted to the hospital due to abnormal uterine bleeding. During the gynecological examination, a 4 cm mass was identified in the cervix. The mass was confined to the cervix without extension to the left or right parametrium, classifying it as Stage IB1 in the FIGO Staging system. Tissue samples were obtained for a Papanicolaou smear and Immunohistochemistry (IHC) testing. The

Papanicolaou smear revealed the presence of malignant cells, and the Immunohistochemistry (IHC) test results indicated neuroendocrine carcinoma. Subsequently, the patient underwent a radical abdominal hysterectomy with pelvic lymphadenectomy and received external pelvic radiotherapy. The disease is currently well controlled, and there has been no recurrence over a span of 15 years.

## DISCUSSION

Neuroendocrine neoplasms (NENs) represent aggressive malignancies that originate from neuroendocrine cells<sup>5</sup>. These malignancies can manifest in various bodily locations, with common occurrences observed in the gastrointestinal tract, pancreas, and lungs<sup>5</sup>. In rare instances, NENs may also manifest in other organs, including the female genital tract<sup>6</sup>. Neuroendocrine cervical carcinoma (NECC) stands as a rare and aggressive histological variant of cervical cancer, carrying an unfavorable prognosis. These tumors exhibit early lymphatic dissemination and a high incidence of distant recurrence. NECC accounts for approximately 1-1.5% of all cervical cancers<sup>7,8</sup>. The mean overall survival for this form of cervical carcinoma is 40 months, with a 5-year survival rate of 34%<sup>5,9</sup>. Consequently, an assertive therapeutic strategy becomes imperative to achieve effective control over both pelvic and distant disease progression.

The biological characteristics of NECC distinguish it from squamous cell carcinoma or adenocarcinoma of the cervix. NECC exhibits a higher propensity to infiltrate the lymphovascular space and disseminate to nearby regional lymph nodes. This malignancy also demonstrates a heightened frequency of both local and distant relapses, resulting in a notably reduced 5-year survival rate of 34%. In stark contrast, squamous cell carcinoma or adenocarcinoma of the cervix presents a higher 5-year survival rate of 65%<sup>5</sup>.

Immunohistochemical (IHC) testing plays a crucial role in confirming the diagnosis of NECC. Diagnostic indicators for NECC encompass neuroendocrine markers such as synaptophysin (SYN), chromogranin (CHG), CD56 (N-CAM), and neuron-specific enolase (NSE). To establish the diagnosis, a minimum of two positive stainings are requisite<sup>5</sup>. Additionally, assessments for p63 and p40 can aid in distinguishing NECC from squamous cell carcinoma. Positive results for p63 and p40 are specific to squamous cell carcinoma<sup>10</sup>.

A well-defined treatment strategy is imperative to effectively manage the disease. Owing to the scarcity of this malignancy, there currently exist no treatment protocols for NECC grounded in prospective clinical trials. Physicians often adopt a multimodal approach, drawing from therapeutic principles applied to cervical cancer at large and insights from neuroendocrine tumor management. The Society of Gynecologic Oncology (SGO) also advocates for this multimodal therapeutic approach, recommending an etoposide/platinum-based chemotherapy regimen for NECC and endorsing radical surgery for early-stage cases, either as a primary intervention or following neoadjuvant chemotherapy. For individuals with advanced-stage disease, the recommendations encompass chemoradiation or systemic chemotherapy, typically involving etoposide and cisplatin. In our case, patients diagnosed with Stage IB1 based on the FIGO staging system underwent radical abdominal hysterectomy accompanied by pelvic lymphadenectomy and external pelvic radiotherapy. Conversely, patients grappling with more advanced stages of the disease were directed towards radiotherapy or exclusively palliative care.

## CONCLUSION

Neuroendocrine neoplasms (NENs) constitute a rare and heterogeneous group of cancers. Among these, Neuroendocrine cervical carcinoma (NECC) stands out as a rare and aggressive histological variant of cervical cancer, characterized by an unfavorable prognosis. As a result, the differentiation of neuroendocrine cervical carcinoma from other potential cervix malignancies becomes crucial. Immunohistochemistry (IHC) tests serve as valuable tools for achieving this distinction. Diagnostic indicators such as synaptophysin (SYN), chromogranin (CHG), CD56 (N-CAM), and neuron-specific enolase (NSE) are particularly relevant for confirming NECC. Additionally, assessments for p63 and p40 can be conducted to differentiate NECC from squamous cell carcinoma, where positive p63 and p40 results specifically point to squamous cell carcinoma. The significance of devising a comprehensive treatment plan for managing these malignancies cannot be overstated. Given the rarity and complexity of NECC, a multimodality treatment approach is highly recommended to attain

improved outcomes. It is vital not only to diagnose and differentiate but also to formulate a tailored treatment strategy to effectively address the challenges presented by NECC.

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