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Small Cell Neuroendocrine Carcinoma of the Cervix: A Case Report and Review of the Literature

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Abstract **Case Report**

Neuroendocrine carcinoma of the cervix (NECC) represents a rare and aggressive subtype of cervical cancer, comprising only a small fraction of cases. Here, we present a case report of a 32-year-old woman diagnosed with small cell NECC, detailing her clinical presentation, diagnostic workup, treatment course, and post-treatment outcomes. Despite its rarity, NECC poses significant diagnostic and therapeutic challenges due to its aggressive nature and distinct biological properties. Histological and immunohistochemical analyses play pivotal roles in diagnosis, with NECC often characterized by positive staining for specific protein markers. Treatment strategies for NECC depend on various factors, including cancer stage, patient characteristics, and tumor biology. While primary radical surgery has shown efficacy for early-stage NECC, advanced cases may necessitate a multimodal approach involving chemotherapy and radiotherapy. We compare our findings with existing literature, discussing the evolving landscape of NECC management and highlighting the need for individualized treatment approaches. Given the scarcity of randomized trials, managing NECC remains a complex endeavor, underscoring the importance of further research and collaborative efforts in optimizing patient outcomes.

Keywords: Cervix, cervical cancer, diagnosis, radical surgery.

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INTRODUCTION

Cancer of the cervix, a frequent malignant tumor in the female reproductive system, is most commonly squamous cell carcinoma (SCC), accounting for over 90% of cases [1]. In contrast, primary neuroendocrine carcinoma of the cervix (NECC) is rare, as neuroendocrine cancers typically occur in the lungs and digestive tracts. NECC makes up only about 1% to 1.5% of all primary cervical cancers [2, 3]. Despite its rarity, NECC is an aggressive form of cervical cancer with a distinct cellular structure. It often presents with symptoms similar to those of more common cervical cancers, such as squamous cell carcinoma and adenocarcinoma. This similarity makes early detection of early-stage NECC particularly challenging [4]. However, NECC stands out from SCC and adenocarcinoma despite sharing similar symptoms. It possesses unique biological properties, translating to a more aggressive cancer with a poor prognosis. Doctors often rely on specific protein markers, like Syn, CgA, and CD56, detected through a technique called immunohistochemistry, to diagnose NECC [5]. Additionally, a protein called p16, which is frequently positive in NECC, might be linked to a specific type of human papillomavirus (HR-HPV) that can cause cancer. NECC is also more likely to have invaded lymphatic channels and spread to nearby lymph nodes at the time of diagnosis compared to other cervical cancers [6, 7]. We report our experience in the management of a case of small cell neuroendocrine carcinoma of the cervix while comparing our data to those in the literature.

PATIENT AND OBSERVATION

A 32-year-old (G4P4) woman with unremarkable medical and family history presented with intermittent light vaginal bleeding for the past two years. The bleeding was not associated with any gastrointestinal, urinary, or other gynecological symptoms. Despite the presence of vaginal bleeding, the patient's overall health status remained stable. Pelvic examination revealed a 6 cm mass involving the cervix and extending into the vaginal fornices, reaching up to the junction of the middle and lower thirds of the vagina. The right and left parametria were also infiltrated. Biopsies from the mass revealed a proliferation of carcinomatous cells arranged in compact sheets, outlining tubulo-glandular formations, and in some areas exhibiting a cribriform pattern. Cyto-nuclear atypias

were moderate, mitoses were few, and the stroma was inflammatory. Immunohistochemical staining of the tumor fragments revealed positive staining of the carcinomatous cells for synaptophysin, neuron-specific enolase (NSE), and chromogranin A antibodies. These findings are consistent with a diagnosis of invasive small cell neuroendocrine carcinoma of the cervix. An MRI and a thoracoabdominal-pelvic CT scan (Figure 1) revealed the presence of a stage IIIB cervical cancer with an enlarged uterus with bosselated contours, displacing the bladder anteriorly, with persistent fatty separation line and impressing the rectum, and with no evidence of deep adenopathy or other signs of tumor extension. The decision made at the multidisciplinary consultation meeting was concurrent chemoradiotherapy. The patient received 5 cycles of chemotherapy one week apart with CDDP (cisplatin or cis-diaminedichloroplatinum) 68mg concomitantly with radiation therapy at a dose of 46 Gray to the pelvis in 30 sessions, 10 Gray to the parametria, and 4 Gray to the lymph nodes. The post-treatment clinical evaluation revealed the persistence of a tumor measuring nearly 3 cm that still infiltrating the vaginal fornices, Therefore, the decision was made to proceed with surgical treatment, which consisted of an extended colpohysterectomy with closure. The postoperative course was uneventful. The pathological examination showed no evidence of malignancy in the surgical specimen, which confirms a good response to neoadjuvant therapy. The patient had an uneventful follow-up for 4 months after the completion of treatment.

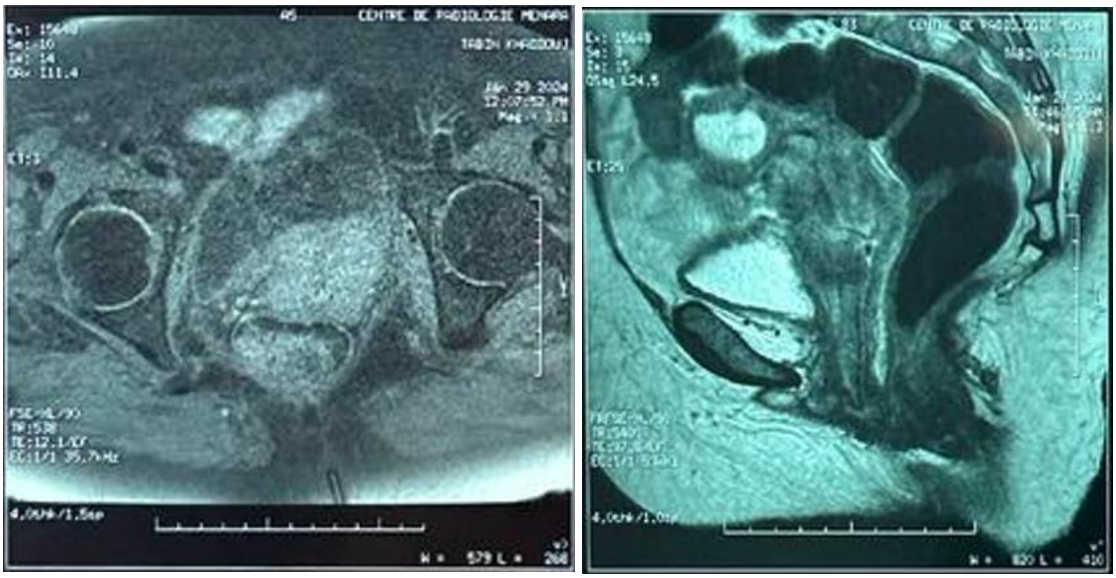

Figure 1: 32-year-old woman with FIGO stage IIIB Small cell neuroendocrine carcinoma of the cervix

DISCUSSION

Neuroendocrine tumors (NET) originate from the embryonic neuroectoderm. Their immunohistochemical profile is similar to cells of endocrine gland [8]. Common sites of involvement are the gastrointestinal tract, pancreas, and lungs [9]. In the cervix, they account for only 0.9 to 1.5% of cervical tumors, which are typically dominated by squamous cell carcinoma [10]. They typically present with symptoms such as postmenopausal vaginal bleeding, abnormal vaginal discharge, postcoital spotting, and a cervical mass. Diagnosis of neuroendocrine cervical cancer (NECC) is primarily based on histological features and immunohistochemical studies. Four main histologic types of NECC are recognized: Typical carcinoid tumors, atypical carcinoid tumors, small cell carcinomas and large cell neuroendocrine carcinomas [12, 13].

Treatment for neuroendocrine cervical cancer (NECC) depends on several factors, including the stage of the cancer, the patient's age and overall health, and the presence or absence of metastases [14]. A 2017 study published in the Journal of Gynecologic Oncology investigated prognostic factors and optimal treatment for stage I and II cervical neuroendocrine tumors (NETs) in 198 patients treated at a Japanese gynecologic oncology center [15]. The study highlights the importance of individualizing treatment approaches for cervical NETs, considering factors such as tumor stage, patient characteristics, and tumor biology. And conclusion was that Primary radical surgery is more effective than radiotherapy alone for stage I and II cervical neuroendocrine tumors (NETs), resulting in lower locoregional recurrence rates. Adjuvant chemotherapy with EP (etoposide + platinum) or CPT-P (irinotecan + platinum) demonstrated favorable outcomes in this patient cohort, achieving high survival rates compared to adjuvant radiotherapy.

Conflicting findings regarding the efficacy of local treatment for stage I and IIA cervical neuroendocrine tumors (NETs): Sheet et al. (1996) Reported a 3-year overall survival (OS) rate of 16% and a 5-year progression-free survival (PFS) rate of 0% for patients with stage I and IIA cervical NETs treated with local therapy (surgery with or without radiotherapy) [16].

Concerning Sevin *et al*., (2000) study the 5-year disease-free survival (DFS) rate was 36%, High incidence of lymph node metastases at diagnosis (40-60%) and Frequent vascular invasion. This results has led to a consensus among experts to combine local therapy with systemic treatment [17, 18].

A key study by Zivanovic *et al.*, compared local treatment alone to local treatment with adjuvant chemotherapy and found a significant improvement in 3-year recurrence-free survival (RFS) for patients receiving chemotherapy. This finding, along with similar results from other studies, has established adjuvant chemotherapy as the standard of care for patients with stage I and II cervical NETs who have undergone local treatment [19]. Chang *et al*., investigated the efficacy of neoadjuvant chemotherapy with VAC/PE (vincristine, doxorubicin, cyclophosphamide, etoposide) followed by hysterectomy in patients with stage I and II cervical NETs. The study reported a favorable response rate, with 6 out of 7 patients achieving a complete response [20]. But the Study by Lee *et al*., Reported no significant survival advantage for patients receiving neoadjuvant chemotherapy, raising questions about its efficacy [21]. For locally advanced tumors (stages IIb-IV) and for inoperable patients, a combination of radiotherapy and chemotherapy is recommended, following the protocol by Hoskins *et al*., [22]. At these stages, a chemotherapy regimen consisting of at least five cycles of cisplatin and etoposide is associated with a better probability of recurrence-free survival. This was the protocol used for our patient, with a clear clinical improvement after neoadjuvant chemotherapy combined with radiotherapy. For advanced stage tumors, they are treated with combination chemotherapy based on platinum agents. In case of recurrence or chemoresistance, a second-line therapy is initiated using vincristine/doxorubicin/ cyclophosphamide and topotecan [23]. In case of metastatic disease or recurrence, chemotherapy, either with cisplatin and etoposide alone or alternating with a VAC-type chemotherapy (vincristine, adriamycin, and cyclophosphamide), is indicated [24].

Generally, according to the recommendations published by Chan *et al*., in 2003 [25] surgical treatment is mainly indicated for NETs classified as I-IIA, measuring less than 4cm, sometimes followed by adjuvant chemotherapy or radiochemotherapy. For tumors classified as I-IIA measuring more than 4cm, neoadjuvant chemotherapy is recommended before surgery. For neuroendocrine tumors of the cervix classified as IIb-IV, radiochemotherapy using the Hoskins protocol is desirable (Figure 2).

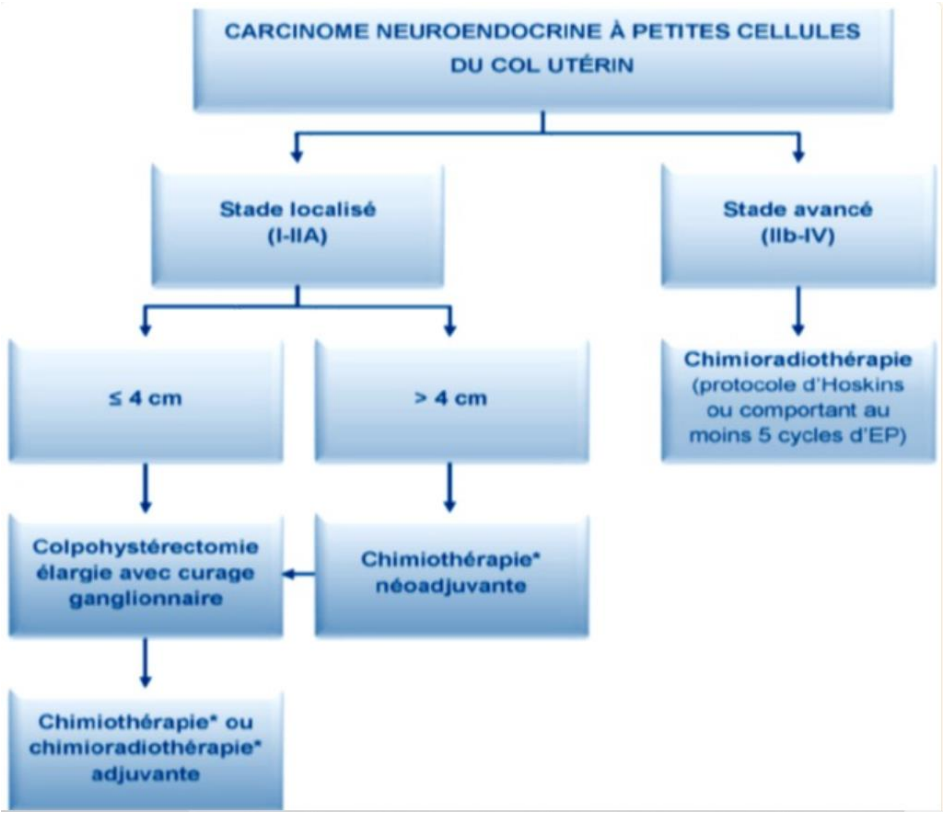

Figure 2: Recommendations for the therapeutic management of neuroendocrine carcinomas of the uterine cervix

CONCLUSION

Neuroendocrine tumors of the cervix are very aggressive and rare tumors, which explains the lack of randomized trials and makes their management increasingly challenging.

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