OPEN ACCESS
Global Journal of Research in Medical Sciences
Volume 02| Issue 01 | Jan-Feb | 2022
Journal homepage: https://gjrpublication.com/journals/
Original Research Article

Neuroendocrine tumor of the uterine cervix: About 2 cases

[1]N. Mekkaoui,* [1]J.Rahmouni, [1]M.K.Saoud, [1]N. Mamouni, [1]S. Errarhay, [1]C. Bouchikhi, [1]A.Banani

[1]Department of Gynecology and Obstetrics I, Hassan II university Hospital, Fez, Morocco

Submission Date: 08th Feb 2022 | **Published Date:** 21st Feb 2022

***Corresponding author:** N. Mekkaoui

Abstract

Neuroendocrine carcinoma is a rare and aggressive tumor, it develops mainly in the lung and in the digestive tract. It represents only 1-3% of cervical tumors. The immunohistochemistry and the histological studies play a crucial role in confirming this type of tumor. The management of these tumors is difficult and essentially based on that of pulmonary neuroendocrine tumors. Their prognosis remains poor.

We report two cases of neuroendocrine carcinoma of the uterine cervix and review the literature on the different aspects of this rare entity.

Keywords: Neuroendocrine Carcinoma, Cervix, Colpohysterectomy, Radiotherapy, Chemotherapy

INTRODUCTION

Neuroendocrine carcinoma of the cervix or small cell carcinoma is a tumor that develops on the cells of the neuroendocrine system and is mainly found in the lungs, pancreas and digestive tract. Its prevalence is 2 cases /100,000[1].

Small cell carcinomas of the uterine cervix are very rare, representing less than 3% of all cervical tumors [2].

We report 2 cases of neuroendocrine tumors of the uterine cervix collected in our department. Through these two recent observations we will review the literature concerning this rare entity.

Case 1

Mrs. N.M aged 48 years, having as antecedent a cholecystectomy 13 years ago, consulted for minimal post-coital metrorrhagia without other accompanying signs evolving for 2 months. Clinical examination found an ulcerative-bourgeous mass at the anterior lip of the cervix making 2cm bleeding on contact. The vaginal walls and parametrium were free. The anatomopathological study of the cervical biopsy was in favour of a neuroendocrine carcinoma.

The immunohistochemical study showed intense and diffuse positive staining to chromogranin, synaptophysin and cytokeratin 7. Pelvic MRI showed an endocervical tumor process of 25*23, bulging into the uterine cervical without evidence of locoregional extension. A thoraco-abdominal scan did not reveal any distant metastases. The tumor was classified as FIGO T1b1No. A radical Ro surgery was performed associating an enlarged colpohysterectomy to the parametrium, a bilateral adnexectomy and a bilateral pelvic curage and lombo-aortic picking. Anatomopathologic study found a 22-mm focus of a small-cell neuroendocrine carcinoma, with hyperchromatic nuclei, a high nucleo-cytoplasmic ratio, high mitotic activity and the presence of numerous peri-tumoral emboli. The curage returned 7 negative nodes on the right and 6 negative on the left. The decision of the multidisciplinary meeting was no indication for adjuvant treatment because of the early stage. Patient remained under surveillance with a good evolution on a 3-month follow-up.

Case 2

Mrs. A.D aged 47 years, with no notable pathological history, consulted for menometrorrhagia evolving for 2 months in a context of weight loss and alteration of the general state. The gynecological examination found a mass expelled from the endocervix making 15 cm, bleeding on contact, and invaded the parametrium bilaterally. The biopsy of the cervix came back in favor of small cell carcinoma of the uterine cervix. A complementary immunohistochemical study of the different fragments showed that the carcinomatous cells were labelled with the following antibodies: anti-synaptophysin, anti-NSE (Neuron Specific Enolase) and anti-chromogranin. This makes this tumor compatible with a poorly differentiated invasive neuroendocrine carcinoma of the uterine cervix. Our patient was diagnosed with locally advanced cervical cancer with invasion of the uterine parameters, classified FIGO IIB. After multidisciplinary meeting the decision

was a concomitant chemoradiotherapy. The evolution was marked in the two months following the beginning of treatment by the occurrence of a clinical and biological infectious syndrome associated with an increase in abdominal volume. The scannographic exploration showed an increase in tumor volume exceeding 20 cm with invasion of ovaries, bladder and rectum, with the presence of pulmonary metastases, and the appearance of several pelvic peritoneal and subperitoneal collections. The final decision of the multidisciplinary committee was to place the palliative protocol and to do a clinical and scannographic surveillance every three months. The patient died four months later.

DISCUSSION

Neuroendocrine tumors are mainly found in the gastrointestinal tract and the lungs. Its localization in the uterine cervix is rare, representing only 1 to 3% of cervical tumors. Clinically, they are manifested by menometrorrhagia and leucorrhoea, and exceptionally by a paraneoplastic syndrome [3]. The diagnosis is based mainly on histological and immunohistochemical study. Endocrine cells have a considerable diversity of size, argyrophilia, immunohistochemical staining and ultrastructure. They can be identified in histochemistry with Grimelius staining by the demonstration of argyrophilic or neurosecretory granulations, in immunohistochemistry by positivity to NSE, chromogranin, synaptophysin and antibodies for gastrin, insulin or by ectopic production of adrenocorticotropic hormone (ACTH), ßMSH, serotonin, histamine and amylose [4]. Small cell neuroendocrine carcinomas are the tumors with the worst prognosis. They have similarities with small cell carcinomas of the lung, as they have a high mitotic index, extensive necrosis, and massive lymphatic and vascular invasion [5]. They are distinguished from squamous cell carcinomas by their higher recurrence rate and the delay in their diagnosis due to the inefficiency of screening for this type of tumor by cervical smear. Staging follows that of all cervical tumors. However, it is important to recognize the increased risk of lymphatic and vascular invasion and the high rate of extra pelvic recurrence. For example, early lymphatic invasion of locoregional adenopathies was found in 40% of stage IB small cell tumors less than 3 cm in diameter. In 60% of these tumors, vascular and lymphatic invasion was observed at the time of diagnosis. The time to recurrence is 19.9 months [6]. Metastases are most commonly bone, supraclavicular and pulmonary. The treatment of cervical neuroendocrine carcinomas is based on that of squamous cell carcinomas, taking into consideration the characteristics of lung neuroendocrine tumors.The treatment of cervical neuroendocrine carcinoma is based on surgery, chemotherapy or radiotherapy. The treatment decision depends mainly on the FIGO stage, tumor size, lymph node staging and the presence or absence of distant metastases [7].

In the absence of trials comparing radiotherapy and surgery, some authors have preferred to integrate them in the framework of a multimodal treatment. By combining surgery, radiotherapy and chemotherapy, Chan et al achieved a five-year survival rate of 32%, which is significantly higher than those reported in the various series. Long-term survivors were patients with tumors less than 2 cm in size who underwent radical surgery [8]. For locally advanced tumors (stages IIb-IV) and for inoperable patients, a combination of radiotherapy and chemotherapy is recommended, according to the protocol of Hoskins et al [9]. In these stages, chemotherapy with at least five courses of cisplatin and etoposide is associated with a better probability of recurrence-free and specific survival.

In the case of metastatic disease or recurrence, chemotherapy, either with cisplatin and etoposide alone or alternating with VAC (vincristine, adriamycin, and cyclophosphamide) chemotherapy is indicated. Prognostic factors were clinical stage, tumor size, presence and number of metastatic adenopathies, small cell histology, and smoking. Clinical stage was the only predictor of survival, 80% in stage I/II, and 38% in stage III/IV. The most common sites of distant relapse were bone and lung (28%) rather than local relapse (13%) [8].

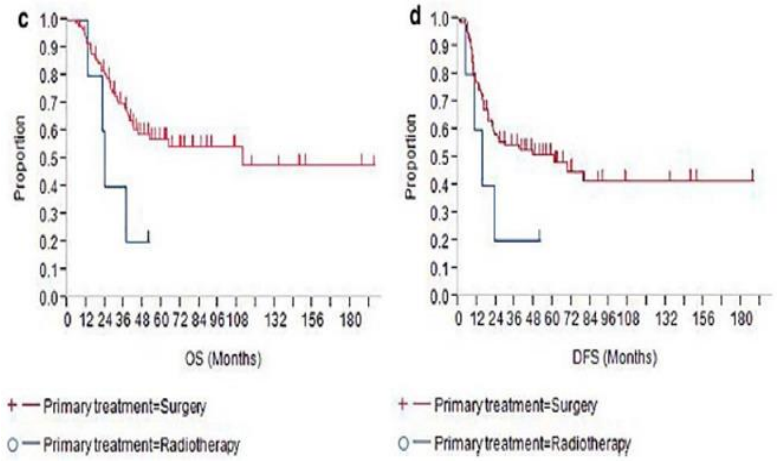

Figure-1: A comparison of survival rate and disease-free survival between two populations, one treated initially with surgery and the other with radiotherapy

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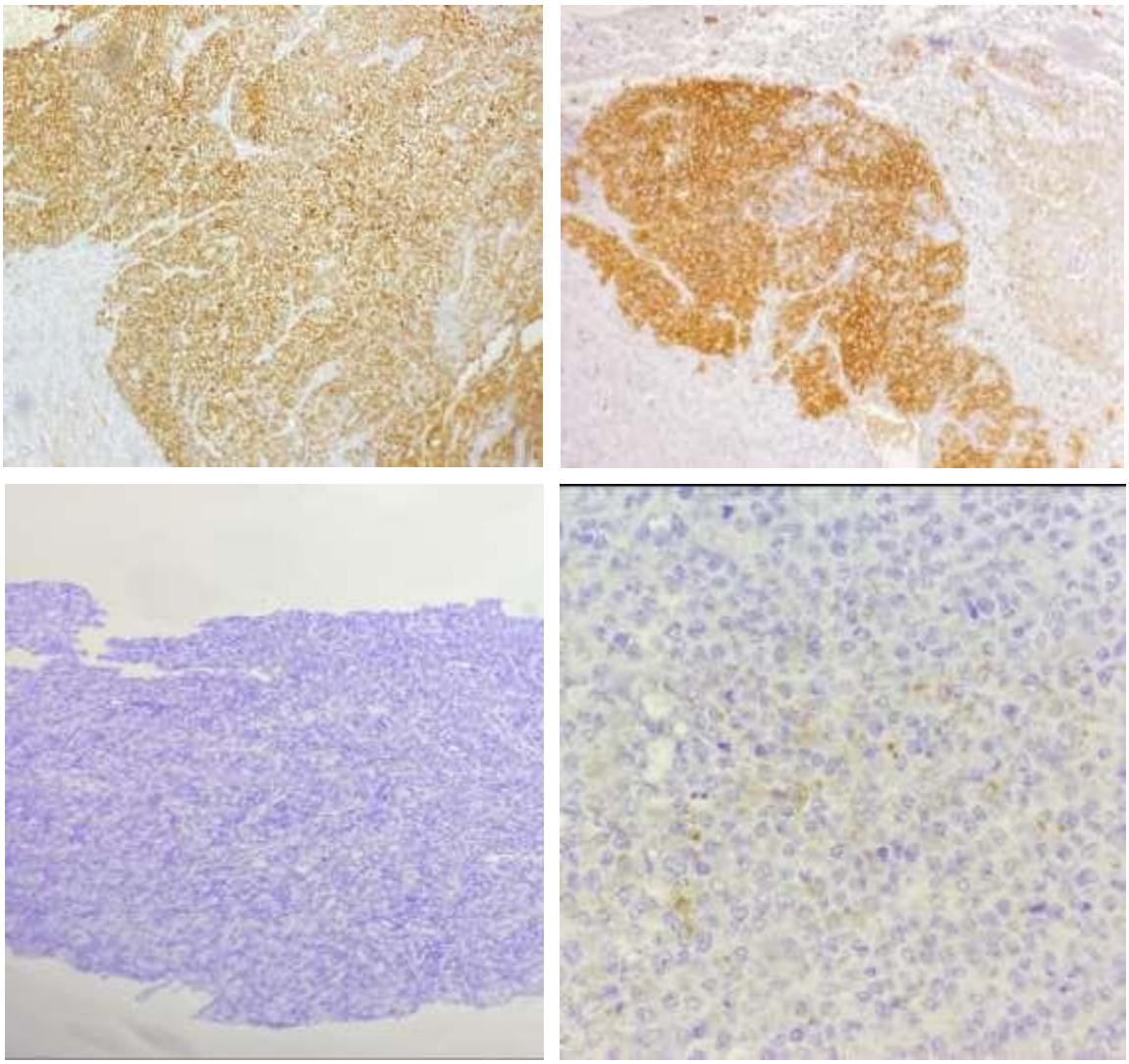

Figure-2: Anatomopathological study shows a tumor proliferation, mostly necrotic, arranged within a thin vascular stroma.The tumor cells are large, with a large nucleus and a scarce cytoplasm basophilic or amphiphilic. Immunohistochemistry shows anti EMA +/ anti synaptophysin + / and anti pancyto-keratin antibodies , in favor of the diagnosis of neuroendocrine carcinoma.

CONCLUSION

Neuroendocrine carcinoma of the cervix is a very rare and aggressive tumor with a poor prognosis. Treatment is based on surgery, chemotherapy or radiotherapy. The prognosis depends mainly on the FIGO stage, tumor size, lymph node staging and the presence or absence of distant metastases. However, to date there is no codified therapeutic consensus, due to the rarity of these tumors and the small number of cases observed.

Figures:

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