

Case Report

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Small Cell Neuroendocrine Carcinoma of the Uterine Cervix to Analysis of 3 Cases

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Abstract

Background: Histopathologically similar to small cell carcinoma of lung, small cell neuroendocrine carcinoma of the cervix is a rare malignancy with an aggressive behavior, due to an early lymphatic involvement and hematogenous dissemination. Pelvic recurrence and distant metastasis are very common. In literature, the best treatment modality remains controversial.

Cases: From a series of 3 cases and a literature review, we focus on screening, prognostic factors and treatment of this cancer.

Conclusion: Human Papilloma Virus (HPV) 18 infection seems to be specifically related to small cell neuroendocrine carcinoma. Screening with HPV genotyping, and a multimodal therapy could improve the prognosis of these patients.

Keywords: Neuroendocrine tumor; Small cell carcinoma; Uterine cervical neoplasm; Human papillomavirus; Pap smear screening

Introduction

Small Cell Neuroendocrine Carcinoma (SCNEC) is an aggressive, rare form of cervical cancer, accounting for less than 3% of all cervical cancers [1-5]. Its extreme rarity represents a limitation in the determination of both effective management and optimal treatment. Previous studies showed that patients with SCNEC treated with a similar modality to the standard treatment for squamous cell carcinoma of the cervix, have a poor prognosis. The histology and clinical behavior of SCNEC is similar to that of small cell lung carcinoma [6]. These tumors are characterized by an early lymphatic involvement and hematogenous dissemination [7]. Early diagnosis is essential. Most therapeutic methods are derived from experiences with neuroendocrine lung tumors, but the survival rate is poor and the best modality of treatment remains controversial.

Case 1

A 39-year-old woman, gravida 2, para 2, was admitted for abnormal vaginal bleeding. The initial clinical examination was normal, but the smear test showed atypical glandular cells consistent with adenocarcinoma. Two weekslater, gynecological and rectal examinations revealed a cervical budding tumor. The pathological diagnosis of a biopsy taken from the uterine cervix was primary adenocarcinoma with a neuroendocrine component. Immunohistochemical study showed a positive reaction to chromogranin a, synaptophysin and neurone-specific enolase. High-risk oncogenic HPV (Human Papillomavirus) type 16 was detected. Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) revealed a lesion of 26×22×24 mm, with infiltration of the vaginal fornix, without lymph node or visceral metastasis. Stage was IIA according to International Federation of Gynecologists and Obstetricians (FIGO) classification.

A lombo-aortic laparoscopic staging was performed. 11 lymph nodes removed and proved to be healthy. Three courses of neoadjuvant chemotherapy with etoposide (100 mg/m²) and cisplatin (100 mg/m²) (J1=J21) were introduced, followed by chemoradiation and uterovaginal low-dose-rate brachytherapy.

On MRI, the tumoral syndrome completely regressed and a radical hysterectomy with bilateral pelvic lymphadenectomy was performed. Histological examination did not find residual lesion. One year after surgery, the patient is in complete remission.

Case 2

A 31-year-old woman, gravida 2, para 2, smoker, presented with abnormal vaginal bleeding with abdominal pain lasting since a few weeks. Speculum examination revealed an ulcerated tumor of the cervical anterior lip. On cytological and histological samples, cells had scant cytoplasm, were small and round shaped with hyperchromatic nuclei. High mitotic activity was seen in the tumor. The immunocytochemical profile demonstrated marker positivity for chromogranin A, synaptophysin and neurone-specific enolase. High-risk oncogenic HPV type 18 was detected (Figure 1). Radiologic evaluations (CT, pelvic MRI, octreoscan) were useful in staging. The solid cervical mass measured 110×76 mm with parametrial and vesical extension, associated with voluminous pelvic and paraaortic lymph nodes (Figure 2). Due to the presence of low back pain, a spinal MRI was performed. Hyposignal T1 diffuse marrow was highlighted, consistent with a neoplasic infiltration of the bone marrow (Figure 2). The diagnosis was confirmed by a biopsy. Final diagnosis was Small Cell Neuroendocrine Cervical Carcinoma (SCNCC); stage IV B according to FIGO classification. The patient received three courses of chemotherapy with etoposide (100 mg/m^2) -cisplatine (100 mg/m^2) (J1=J21). Tolerance was poor with significant hematologic toxicity responsible for an episode of neutropenic colitis. On MRI control, the

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Page 2 of 3



Figure 1: Cervical biopsy (hematoxylin and eosin, 4x) (a) in case 2 revealing small irregular cell with hyperchromatic nuclei and scanty cytoplasm (hematoxylin and eosin, 400x) (b). Immunocytochemical reaction are positive for synaptophysin (c), chromogranin A (d) and neurone-specific enolase (e). Malignant cells infected by oncogenic HPV (in situ hybridation) (f).



Figure 2: Pelvic MRI before treatment: cervical tumor of $11 \times 7,6$ cm (sagittal T2) (a), pelvic and paraaortic lymph nodes (coronal T2) (b). Spinal IRM: diffuse marrow hyposignal (sagittal T1) (c). Pelvic MRI after chemotherapy: tumor regression (sagittal T2) (d).

size of the cervical tumor had significantly decreased (90% decrease); para-aortic and pelvic lymph nodes also disappeared. Malignant cells were no longer present on bone marrow biopsy. Three additional treatments were prescribed in combination with para-aortic and pelvic radiotherapy. Taking into account the initial stage of the disease, the indication of surgery is not retained (in consultation with the team of the Gustave Roussy Institute in Villejuif). After 2 months, she developed brain metastases and died of the disease.

Case 3

A Pap smear screening performed during the post-natal consultation has highlighted the Cervical Intraepithelial Neoplasia (CIN) III, positive HPV, in a 30-year-old woman, gravida 1, para 1. The uterine cervix was macroscopically normal. The patient was not submitted to colposcopy appointment, and was admitted 4 months later, for abnormal vaginal bleeding. A cervical lesion of 2 cm was clinically demonstrated. Colposcopy-directed biopsy of the mass revealed a malignant epithelial tumor with neuroendocrine differentiation. (Positive immunoreactivity for neurone-specific enolase and synaptophysin, but negative for chromogranin A). MRI of the pelvis showed a cervical neoplasm of $24 \times 31 \times 40$ mm extended to upper two thirds of the vagina, without lymph node metastasis. Cells

were infected with HPV type 16 and 18. The SCNCC was defined as stage II A1.

The patient underwent a radical hysterectomy with bilateral adnexectomy and pelvic lymphadenectomy. Histopathological examination of the specimen revealed a solid mass with ill-defined borders. Diffused lymphovascular space involvement was found. Parametria and lymph nodes were unaffected by the cancer.

Three courses of adjuvant chemotherapy with etopisde (100 mg/ m^2)-cisplatine (100 mg/m²) (J1=J21) were performed. Then the patient received 50 Gy whole pelvis radiations with concomitant cisplatin weekly. After external radiotherapy, vaginal brachytherapy was administered using the highdose- rate brachytherapy (15 Gy). She tolerated well the treatment with no significant side effects. Four years after the end of the treatment, no recurrence of the disease could be demonstrated.

Discussion

Neuroendocrine tumor of the uterine cervix is a very rare neoplasia, accounting for 1-3% of all cervix cancers [1-3]. Histopathologically, neuroendocrine cervical carcinoma resembles small cell carcinoma of the lung and is classified in neuroendocrine pulmonary tumor published by the World Health Organization.

Although the etiology and pathogenesis of SCNCC are unknown, some reports suggest that SCNCC might be strongly associated with high-risk oncogenic HPV. HPV 18 would be a viral type specifically associated with cervical small cell carcinoma [4].

Clinicopathological characteristics such as smoking, tumor size, number of involved lymph nodes and neuroendocrine histology pure, would be poor prognostic factors. Only FIGO stage and lymph node status were significant indicators for survival.

Earlier diagnosis may improve the survival rate of these patients. According to recent studies, the diagnostic accuracy of cytologic smears in diagnosing SCNCC is low, reaching approximately 20% [5]. Neuroendocrine malignant cells develop in the basal layers of the epithelium, preferably in the upper part of the cervical canal. They have the ability to pass the basement membrane while preserving the superficial layers of the epithelium. The Pap smear screening might not be helpful in early diagnosis of SCNCC. Systematic detection of HPV could be a valuable aid in the detection of SCNCC [5].

In the series of Straughn et al. [8], patients whose tumors were positive for chromogranin had a significantly poorer survival rate than those for who tumors were chromogranin negative.

This neoplasia is extremely aggressive due to the early development of lymph node metastasis and vascular invasion.

Treatment of SCNCC remains controversial due to the high rate of recurrence and the premature development of metastases, even with early-stage disease. The 5-year survival rates range from 31.6 to 46.6% for early-stage disease and from 0 to 14% for advanced-stage disease [1,8,9]. The usual treatment for early-stage is radical surgery without para-aortic lymphadenectomy, but indications for this treatment should be limited.

Combination chemotherapy is considered by many authors to be essential for the appropriate management of small cell carcinoma of the uterine cervix, as in the treatment of small cell lung cancer. The administration of chemotherapy similar to that for small cell lung carcinoma (as etoposide-cisplatin or irinotecan-cisplatin) improves the survival of patients [6]. Pelvic radiotherapy can control locally the disease. Chemotherapy products not passing the blood-brain barrier, the brain prophylactic irradiation is an option (20 Gy brain in toto). The benefit of para-aortic lymphadenectomy remains unproven. In the literature, only few patients have benefited of it.

In conclusion, the small cell carcinoma of the uterine cervix seems to be a very chemosensitive tumor. Therefore, chemotherapy can be used as an adjuvant or adjuvant to control the disease in its entirety, while surgery and radiotherapy are thought to control local and regional disease. Despite the retrospective studies and case reports published in the literature, the best modality of treatment remains controversial.

As in lung cancer, molecular biology could be beneficial to develop targeted therapies in order to improving the prognosis of patients.

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Page 3 of 3