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REVIEW ARTICLE

NEUROENDOCRINE CARCINOMA OF THE CERVIX: ABOUT 2 CASES AND REVIEW OF THE LITERATURE

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ABSTRACT

Neuroendocrine small cell carcinoma of the cervix is a malignant and rare tumor representing less than 3% of all cervical tumors. The diagnostic and therapeutic management of these tumors is difficult and is essentially modeled on that one of pulmonary neuroendocrine tumors. Like the latter and despite multimodal treatment, their prognosis remains unfavorable. We report 2 new cases of small cell cervical neuroendocrine carcinoma and through the giving facts of the literature we will focus on the different aspects of this rare entity.

INTRODUCTION

Neuroendocrine carcinoma is a rare and aggressive malignancy. Developing mainly at the expense of the bronchial tree and the digestive tract. Neuroendocrine carcinomas with small gynecological cells are unusual. Their prognosis is overall bleak. The morphological characteristics, the clinical aspects and the therapeutic management of these tumors are comparable to the neuroendocrine tumors of the lung.

Case presentation

Case 1: A 62-year-old woman, 4th gesture 4th parte, menopausal for 14 years having as antecedent multinodular goiter, thyroidectomized under Levothyrox in euthyroidie, consulting for metrorrhagia of low abundance. Speculum examination reveals a localized burgeoning and infiltrating lesion in the posterior cervical lip, 1.5 cm long. The histological and immunohistochemical study of the biopsy material revealed a small cell neuroendocrine carcinoma that expresses CKAE1 / AE3, EMA, synaptophysin and chromogranin, strongly TTF and Ki67%; and focally the CD56 (Figure 1, Figure 2).

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Pelvic magnetic resonance imaging (MRI) showed a cervical tumoral process measuring 20 mm long axis, remaining confined to the cervix without locoregional extension and without adjacent lymphadenopathies, the extension assessment was negative (Figure 4). The tumor was classified as Stage IB according to the classification of the International Federation of Obstetrics Gynecology (FIGO). The biological assessment revealed a fluctuating neutropenia between 880 and 500, the demargination test was considered positive and the patient was under biological surveillance. A concomitant radio chemotherapy was administered weekly with cisplatin 40mg / m2 alone due to neutropenia, concomitant with external radiotherapy by 18mV photons on the uterine cervix by 4 fields at a total dose of 46Gy, 2Gy per fraction in 23 sessions, thereafter she benefited from a radical surgery (R0) by enlarged colpohysterectomy with bilateral pelvic lymphadenectomy, whose anatomopathological study of the operative specimen showed a minimal tumor residue of little differentiated carcinoma, infiltrating the chorion at about 7mm depth, the surface invasion is not assessable given the fragmented and dispersed nature of the tumor residue, the uterine wall, the vaginal collar, the parameters, the fallopian tubes and the ovaries are free from any tumor infiltration, with absence of vascular emboli or peri-nerve wrapping, left pelvic lymphadenectomy is negative (13N- / 13N), right pelvic lymphadenectomy is also negative (13N- / 13N), and the tumor

is stadified: ypT1BN0M0. The surgery was followed by 2 weekly sessions of 10Gy barrier brachytherapy, a new postoperative radiological extension assessment was performed, showing a low abundance intraperitoneal effusion with individualization of some peritoneal nodules under the hepatic system and at the level of the left parietocolic gutter and the douglas cul de sac, chemotherapy was given based on cisplatin 80mg / m2 on day 1 combined with etoposide 100 mg / m2 from day 1 to day 3, one treatment every 3 weeks. After 3 courses of chemotherapy, the radiological evaluation showed a disappearance of ascites and peritoneal nodules, without evolutionary disease, hence the decision to add 3 other chemotherapy and then the patient was put under surveillance. The evolution was marked by complete remission of the disease with a retreat of 24 months.

Case 2: 59-year-old woman, 7th gesture 7th parity, menopausal for 9 years, without significant pathological antecedent, the beginning of the symptomatology started from three months by post coital metrorrhagia with dyspareunia, the physical examination finds a patient in good general condition, the examination of the cervix reveals an ulcerative-budding tumor process 6 cm invading the 1/3 sup of the vagina, the parameters infiltrated in distal and ganglionic areas are free. The histological and immunohistochemical study of the biopsied material revealed a small cell neuroendocrine carcinoma of the cervix that weakly expresses synaptophysin and moderately CD56. Pelvic MRI showed a tumor process in the cervix extended intra-cavitary, a left lateral adenomegaly uterine about 4.3 cm, a compartmentalized effusion at the level of the left iliac fossa about 5.8 cm, and a disappearance of fat in places between the neck and the rectum with integrity of the fat between the neck and the bladder. The proctological examination showed anterior bulging of the rectum with a healthy mucous membrane. The extension assessment was negative. The tumor was classified IIIC1 according to the classification of the International Federation of Obstetric Gynecology 2018 (FIGO). Concomitant radiochemotherapy was given weekly with cisplatin 40mg / m2, concomitant with external beam radiation at 46 Gray, 2Gy per fraction in 23 sessions on the pelvis, a Boost of 10 Gray, 2Gy per day. Fraction in 23 sessions, on the parameters and a boost of 10 Gray, 2Gy per fraction in 23 sessions, on adenopathies. Radiotherapy was followed by uterovaginal brachytherapy at a dose of 28 Gy in 4 fractions of 7 Gy, with a partial response, on pelvic MRI which objectified a cervical-centered tissue process of 31 * 29mm with fluid retention. Upstream, then the patient was referred for hysterectomy closure after performing a new extension assessment, but challenged, since the thoraco-abdominopelvic computed tomography scanner (CT scan) showed diffuse peritoneal carcinomatosis with pulmonary metastases. The evolution was marked by the deterioration of the general state and the installation of an abdominal distension with edema of the lower limbs taking the bucket. Doppler echo of the lower limbs returning to deep venous thrombosis, and the patient was put on anticoagulation at a curative dose, the patient subsequently died following the progression of her disease, is eight months from the time of diagnosis.

DISCUSSION

Neuroendocrine small cell carcinoma of the cervix is a rare malignant tumor that represents less than 3% of cervical tumors, mostly are squamous cell carcinomas

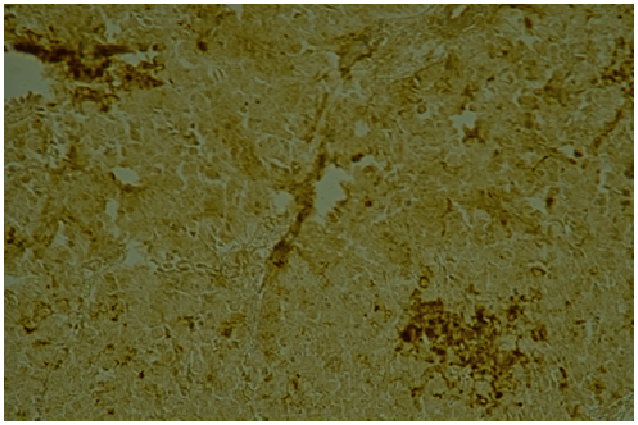

Figure 1. Immunohitological stady: Granular cytoplasmic staining of tumor cells by anti-synaptophysin antibody (x20)

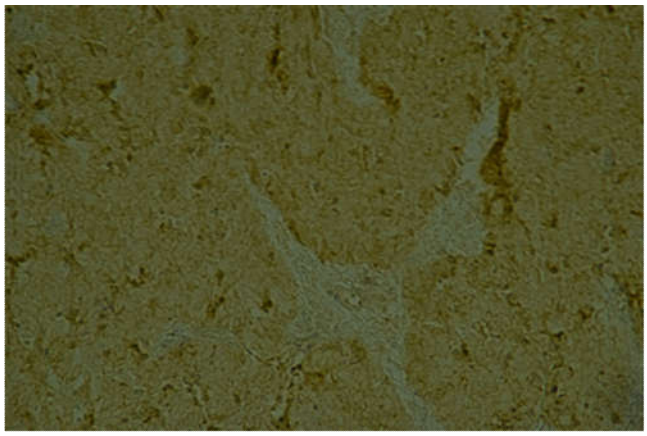

Figure 2. Immunohitological stady:Granular cytoplasmic staining of tumor cells by anti-chromogranine Aantibody(x 20).

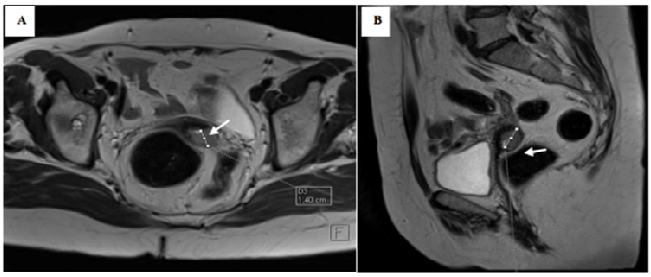

Figure 4. Pelvic MRI in axial T2 (A), sagittal T2 (B) sequence: Tumor process of 20x14 mm centered on the cervix and confined to the latter without extra uterine extension

(Albores-Saavedra, 1997; McCusker, 2003). Described for the first time in 1957 (Reagan, 1957). They originate in the cells of the neuroendocrine system, and can develop in several sites of the body including the digestive tract, pancreas and lung. Their actual incidence is probably underestimated because it is described under different terminologies such as carcinoid tumor, argyrophilic cell carcinoma, apudoma, oat grain cell carcinoma, neuroendocrine carcinoma, atypical carcinoid, undifferentiated small cell carcinoma, or carcinoma. Intermediate cells (Reagan, 1957; Albores-Saavedra, 1997; McCusker, 2003). In 1997 and for the sake of homogenization, Albores-Saavedra *et al*. proposed a classification of neuroendocrine tumors into four subtypes, namely small cell neuroendocrine carcinomas, the most common characterized

by high mitotic activity, extensive necrosis, vascular invasion and which are frequently associated with human papillomaviruses. Other subtypes are large cell neuroendocrine carcinomas and differentiated neuroendocrine tumors, typical and atypical carcinoid tumors (Albores-Saavedra, 1997). These tumors occur at a median age of 42 years (20-87) (McCusker, 2003; Cohen, 2010), which appears younger than for squamous cell carcinoma of the cervix. Clinical symptomatology is nonspecific, and the most common signs are vaginal bleeding and leucorrhea. Since small cell neuroendocrine carcinomas are most often undifferentiated, paraneoplastic syndromes (Cushing's syndrome, carcinoid syndrome, hypoglycaemia, syndrome of inappropriate antidiuretic hormone secretion, hypercalcemia) are exceptional (Delaloge *et al*., 2000; Kothe, 1990).

Like squamous cell carcinoma of the cervix, these tumors are classified according to the FIGO classification. They are often diagnosed later than squamous cell carcinoma of the cervix (McCusker, 2003), because unlike the latter, who see their incidence and the number of advanced tumors at the time of diagnosis decrease through cervicovaginal smear, the latter is ineffective for screening. Small cell neuroendocrine carcinomas (Wang, 1998; Zhou, 1998). The diagnosis is based on histological examination and more particularly on the immunohistochemical study by the demonstration of at least one neuroendocrine marker (synaptophysin, chromogranin A, specific enolase neuron) which allows the diagnosis (Gardner, 2011; Van Nagell, 1988). On macroscopic examination, the tumor is readily endocervical. Two main forms are observed: the massive nodular form slightly attached to the cylindrical mucosa and the multi-micronodular basaloid tumor. Histologically, neuroendocrine carcinomas show a histological spectrum ranging from a typical or atypical carcinoid tumor to small cell carcinoma. Endocrine cells possess considerable size, argyrophilicity, immunocytochemical staining, and ultrastructure. They can be identified in histochemistry (Grimelius staining) in ultrastructure by the demonstration of argyrophilic or neurosecretory granulations, in immunocytochemistry by NSE positivity, chromogranin, synaptophysin and antibodies for gastrin, insulin or by ectopic production of ACTH, βMSH, serotonin, histamine, amylose.Mannion *et al* compared the microscopic characteristics and the survival rate of the four categories; small cell carcinomas were worse prognoses with similarities to small cell carcinomas of the lung. They are characterized by a high mitotic index, extensive necrosis, and massive lymphatic and vascular invasion with a strong association with HPV18 (Mannion, 1998). Due to the high propensity for regional and metastatic dissemination, the initial assessment should include abdominopelvic imaging, preferably magnetic resonance imaging (Gardner, 2011). In a data analysis of the Surveillance Epidemiology and End Results (SEER) program covering a 15-year period (1983 to 1998), McCusker *et al*. found a ganglionic invasion rate of 57% for small cell neuroendocrine carcinomas versus 18% for squamous cell carcinomas (McCusker, 2003). For the latter, recent imaging techniques have made it possible to improve ganglion staging, in particular with positron emission tomography (PET), which has shown its superiority in this indication both at the pelvic level (67% versus 20%). than lumbar-aortic (21% vs. 7%). Positron emission tomography-Scan (PET-scan) is regarded as a standard examination in the extensional evaluation of squamous cell carcinoma of the uterine cervix above IB2, and for some authors for less advanced tumors (Bonardel, 2009). For small-cell neuroendocrine carcinomas of the cervix, PET-scan may also find indications for localized tumors: 20% of stage IB1 tumors reach the pelvic ganglia, and this rate is more than 50% if the stage is greater than IB2 (McCusker, 2003; Kuji, 2013). Moreover, extrapelvic metastases are present at the time of diagnosis in about 25% of cases and are mainly pulmonary, bone and supraclavicular, even in the absence of pelvic lymphadenopathy (McCusker, 2003; . Zivanovic, 2009; Gardner, 2011; Hoskins, 2003). To our knowledge, there is only one retrospective series evaluating the value of PET-CT in cases of small cell carcinoma of the cervix. This included five patients, and PET-CT revealed metastases in two patients, thus changing the therapeutic management (Lin, 2012). Therefore, this review could be of interest in the pretreatment assessment of small cell neuroendocrine carcinomas. In the recommendations of Gardner *et al*., PET-CT can be proposed because of the high rate of metastases. Brain imaging is only necessary if there are signs of call or lung metastases (Gardner, 2011; Bonardel, 2009; Viswanathan, 2004). 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 lymphadenopathies was observed in 40% of IB stages of 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 recurrence time is 19.9 months (Van Nagell, 1988). Metastases are more commonly bone, supraclavicular and pulmonary.

Since small cell neuroendocrine carcinomas of the cervix are rare, there is no randomized study evaluating their treatment. The only two prospective series total 33 patients and do not allow definitive conclusion (Morris *et al*., 1992; Chang, 1988). Also, their treatment is modeled on that of other cervical tumors, while cosidering the characteristics and experience gained from lung neuroendocrine tumors. In case of localized tumor (stage I-IIA), it appeared very early that despite local treatment of the primary tumor, the majority of patients saw metastases develop, the main cause of death within three years. Two authors reported the disappointing results of local treatment alone (surgery with or without radiotherapy) in case of localized tumor. Sheets *et al*., The first, found a three-year overall survival rate of 16% and a five-year progression-free survival rate of 0% (Sheets, 1988). For Sevin *et al*., The latter was 36% (Sevin *et al*., 1996). Relapses mainly haematogenous (67 to 90% of cases) and ganglionnaires (34% of cases), a high incidence of lymphadenopathies at diagnosis (40-60%), and a frequent vascular invasion, were all factors that prompted the majority of authors to associate systemic treatment with local treatment (Kuji, 2013; Morris, 1992; Lewandowski, 1993). Three studies retrospectively compared local treatment alone (surgery) and local treatment with adjuvant chemotherapy. Thus, Zivanovic *et al*. found a three-year recurrence-free survival rate of 83% for patients who received cisplatin and etoposide-based chemotherapy versus0% for local treatment alone (Zivanovic, 2009). An analysis of a larger Japanese series of 52 patients also showed the benefit of chemotherapy for both the progression-free survival rate and the overall survival rate (Kuji, 2013). Finally, in Cohen *et al*.'s series, there was certainly a survival benefit for adjuvant chemotherapy (47.8% versus 38.7%), but this difference did not reach the

level of significance (Cohen *et al*., 2010). Because of the early metastatic spread rate, some authors have preferred to use neoadjuvant chemotherapy. Morris *et al*. reported their experience with the management of ten stage IB-IIB tumors by surgery or radiotherapy preceded by chemotherapy. The response rate was 57% with a median survival time of 28 months (Morris *et al*., 1992). Bermudez *et al*. found a partial response in 69.4% of cases, and complete in 15.3%. Moreover, the presence of a tumor residue greater than 2 cm after chemotherapy was predictive of the overall survival rate, which was 58% if it was less than 2 cm, and 21% if not (Bermúdez, 2001). Lee *et al*., The only ones, found a deleterious effect of neoadjuvant chemotherapy compared to adjuvant chemotherapy (Lee, 2008). Thus, while the role of chemotherapy seems to be established, the sequence and type of chemotherapy are less so. The different regimens used in the retrospective studies are very heterogeneous, and extrapolated from series on lung cancer. The combination of etoposide and cisplatin has proved superior to lung neuroendocrine carcinomas and is now preferred to other chemotherapies.

In the case of a localized tumor, the preferred local treatment is surgery, with or without radiotherapy. Only Hoskins *et al*. preferred him radiotherapy and obtained very encouraging results. In this series, two protocols were used. The first (from 1988 to 1995) included first-line chemotherapy followed by cisplatin/etoposide chemoradiotherapy. The second (from 1996 to 2002) included neoadjuvant chemotherapy with paclitaxel/ carboplatin, followed by chemoradiotherapy and adjuvant chemotherapy. Prophylactic brain irradiation was optional during the first years and then discontinued in 1998. The results obtained were very promising, with a three-year progression-free survival rate of 80%, and overall and recurrence-free survival rates of 60% and 57%, respectively. It should be noted that the stage used was radiological thus making comparison with other series difficult (Hoskins, 2003). In the absence of trials comparing radiotherapy and surgery, some authors preferred to integrate them as part of a multimodal treatment. Combining surgery, radiotherapy and chemotherapy, Chan *et al*. managed to obtain a five-year survival rate of 32%, which is significantly higher than those reported in the various series. Long-term survivors were those with tumors less than 2 cm in size and has underwent radical surgery (Chan *et al*., 2003). In 2013, Mc Cann *et al*. achieved cure of all stage I tumors by combining neoadjuvant chemotherapy with surgery followed by adjuvant therapy (chemotherapy or mostly chemoradiation). In the group of patients treated by first-line surgery, and excluding a patient with an initially unresectable disease, only one tumor recurred (in the absence of adjuvant chemotherapy). In addition, they recommended neoadjuvant chemotherapy in the event of a large tumor, which enabled them to obtain complete responses in four of their six patients with tumors larger than 2 cm (three of them from 8 to 11). cm) (McCann *et al*., 2013). In the series of Hoskins *et al*. mentioned, and according to the authors, two of the four pelvic recurrences could have been avoided by surgery (Lin *et al*., 2012). The analysis of a single series of 34 patients did not find any benefit in adjuvant radiotherapy. It should be noted that it was not clear whether the patients had concomitant chemotherapy (Chan *et al*., 2003). For locally advanced tumors (stages IIb-IV) and for inoperable patients, an association of radiotherapy and chemotherapy is recommended, according to the protocol of Hoskins *et al*. (Gardner, 2011; Hoskins, 2003). At these stages, chemotherapy with at least five courses of cisplatin and etoposide is associated with a better probability of recurrent-free survival and specific (Wang, 2012). In cases of metastatic disease or recurrence, chemotherapy with either cisplatin and etoposide alone or alternating with VAC chemotherapy (vincristine, adriamycin and cyclophosphamide) is indicated (Gardner, 2011). For pulmonary neuroendocrine carcinomas, prophylactic brain irradiation in case of response is the rule. Weed *et al*. found in their series a high incidence of brain metastases (25%) and therefore proposed prophylactic irradiation in patients with cervical neuroendocrine carcinoma (Weed, 2003). In contrast, Hoskins, *et al*., In 14 years did not find synchronous cerebral metastases or in the absence of lung metastases, leading them to change their attitude: prophylactic irradiation that was optional in the older protocol, because of this, was abandoned in the most recent (Hoskins *et al*., 2003). To date, there is insufficient evidence to recommend prophylactic irradiation for cervical neuroendocrine tumors (Gardner, 2011; Naidoo, 2013). The prognosis for these tumors remains unfavorable, with a five-year overall survival rate of 36.8% at stages I-IIA and 8.9% at stages IIb-IV, which is significantly lower than observed with squamous cell carcinoma of the cervix (Cohen *et al*., 2010). Several authors have tried to determine the prognostic factors associated with survival in cervical neuroendocrine carcinoma. The tumor stage is found in the three largest published series. Other factors that emerge from these series are age, race, presence of pelvic adenopathies, primary surgery for localized tumors, and adjuvant chemotherapy or chemoradiotherapy for advanced tumors (Cohen *et al*., 2010; Hoskins *et al*., 2003; Wang, 2012; Chen, 2008). In our first patient, the tumor was classified at the time of diagnosis stage I1BN0M0. She was able to survive with tumor sterilization after radiation chemotherapy, surgery and brachytherapy with a retreat of 24 months. Unlike the second patient, who had a tumor classified at the time of stage IIBNoMo diagnosis; She was able to survive only eight months after concomitant chemoradiotherapy followed by uterovaginal brachytherapy, and died by progression of her disease before the scheduled date of surgery.

Conclusion

Neuroendocrine small cell carcinoma of the cervix is very rare. The diagnosis of certainty is based on histopathological and immunohistochemical study. There is no consensus for optimal treatment, multicenter clinical trials are needed to try to determine an univocal and effective treatment, to improve the survival of these patients.

Abbreviations

MRI: Pelvic magnetic resonance imaging.

FIGO: International Federation of Obstetrics Gynecology.

CT scan: Computed tomography scanner.

SEER: Surveillance Epidemiology and End Results.

***PET-scan*:** Positron emission tomography-scan.

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