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Neuroendocrine Tumors Of The Cervix: Case Study And Literature Review

El Baraka Yassine; Achkif Salaheddine . Saoud Karam, Mamouni Nisrine, Errarhay Sanaa, Bouchikhi Chahrazed, Banani Abdelaziz

Gynecological obstetrics department, hospital university Hassan II, FEZ.MOROCCO

Abstract : *Neuroendocrine carcinoma is a rare and aggressive malignant tumour, mainly developing at the expense of the respiratory and of the digestive tract. Gynecological neuroendocrine tumours are rare and small cell neuroendocrine tumours of the uterine cervix represent 3% of cervical cancer. Given their rarity and the lack of randomized trials, the diagnostic and therapeutic management of these tumors is difficult and essentially based on that of pulmonary neuroendocrine tumours. Like the latter, and despite mul-timodality regimens, the prognosis of these tumours remains poor.*

Keywords : small cell neuroendocrine carcinoma; cervix; diagnosis; treatment; prognosis

Introduction :

First described in 1957 [1], small cell neuroendocrine carcinomas of the cervix are rare tumors, accounting for less than 3% of cervical tumors [2-4]. They have common characteristics with squamous cell carcinomas of the cervix, but also have characteristics that are specific to small cell neuroendocrine carcinomas, such as loss of heterozygosity, early lymph node involvement ... [2,5,6]. These tumors also have a very poor prognosis, and at the same stage, survival compared to squamous cell carcinomas of the cervix is much lower [4]. Due to their rarity, there are no randomized studies evaluating their treatment, which is largely based on experience with both cervical and lung tumors. It soon became apparent that local treatment alone (surgery or radiotherapy) was associated with a high rate of recurrence, especially hematogenous recurrence, leading most authors to combine it with systemic treatment [3,7-11]. Despite this multimodal treatment, the prognosis for neuroendocrine carcinomas is still poor [3,7-11]. less unfavorable [4].

we report an observation of small cell neuroendocrine carcinoma of the cervix and review of the literature .

Observation :

Mrs. I.Y, 50 years old diabetic, consulted for minimal metrorrhagia without other accompanying signs. The clinical examination found a cervical tumor with a vagina and free parameters. Biopsy with pathology study was in favor of a small cell neuroendocrine carcinoma. Pelvic MRI objectified a tumor process of the posterior lip of the cervix without any sign of locoregional extension. The extension assessment performed (thoracoabdominal CT scan) was normal. The tumor was classified as T1b1NoMo according to the classification of the International Federation of Gynecology and Obstetrics (FIGO). Radical surgery was performed combining an enlarged colpohysterectomy, bilateral adnexectomy and pelvic curage. An anatomopathological study of the operating room found a 22 mm focus of a small cell neuroendocrine carcinoma, with hyperchromatic nuclei, a high nucleo-cytoplasmic ratio. Curing brought back 10 negative lymph nodes on the right and 7 negative on the left. The adjuvant treatment consisted of external radiotherapy at a dose of 45Gray (Gy) on the pelvis, in 25 fractions at 1.8 Gy per fraction and 5 fractions per week over 35 days, followed by 2 sessions of vaginal brachytherapy and chemotherapy with cisplatin and etoposide.

Discussion :

Neuroendocrine carcinoma is a rare and aggressive malignant tumor, developing primarily at the expense of the bronchial tree and digestive tract. It accounts for only 1-3% of cervical tumors, the majority of which are squamous cell carcinomas [2-4].

Identified in 1957 for the first time, its actual incidence is probably underestimated because it is described under different terminologies such as carcinoid tumor, argyrophilic cell carcinoma, apudoma, ... [1,2,4]. 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 frequent ones characterized by high mitotic activity, extensive necrosis, vascular invasion and which are frequently associated with human papillomaviruses .

During the last two decades, and in contrast to squamous cell carcinomas of the cervix, an increase in the incidence of small cell neuroendocrine carcinomas has been observed, reflecting the use of this common terminology, and the publication of retrospective series has highlighted several unique features [4,12].

These tumors occur at a median age of 42 years (20-87), [4,11] which seems younger than for squamous cell carcinomas of the cervix. The clinical symptomatology is non-specific, and the most frequently found signs are vaginal bleeding and leukorrhea.

Like squamous cell carcinomas of the cervix, these tumors are classified according to the Figo classification. They are often diagnosed later than squamous cell carcinomas of the uterine cervix [4], because unlike squamous cell carcinomas of the uterine cervix, where the incidence and number of advanced tumors at the time of diagnosis is reduced by screening, the CSF is ineffective for the detection of small cell neuroendocrine carcinomas ...

Cervical biopsy often finds an undifferentiated type of tumor, and it is the presence of at least one neuroendocrine marker that allows diagnosis [10]. Because of the strong propensity for regional and metastatic spread, the initial workup should include abdominal pelvic imaging, preferably magnetic resonance imaging [10]. In an analysis of data from the Surveillance Epidemiology and End Results (SEER) program covering a 15-year period (1983 to 1998), McCusker et al. found a lymph node invasion rate of 57% for small cell neuroendocrine carcinomas versus 18% for squamous cell carcinomas [4]. For the latter, recent imaging techniques have made it possible to improve lymph node staging, particularly with positron emission tomography (PET), which has shown its superiority in this indication at both pelvic (67% versus 20%) and lumbo-aortic (21% versus 7%) levels.

In addition, extra pelvic metastases are present at diagnosis in approximately 25% of cases and are predominantly pulmonary, bony, and supraclavicular, even in the absence of pelvic lymphadenopathy [4,8,10]. To our knowledge, there is only one retrospective series evaluating the value of PET-scanography in small cell neuroendocrine carcinoma of the cervix.

This series included five patients, and PET scans revealed metastases in two patients, thereby modifying therapeutic management. Therefore, this examination could be of interest in the pre-therapeutic evaluation of small cell neuroendocrine carcinomas. In the recommendations of Gardner et al. PET-scanography can be proposed due to the high rate of metastasis. Brain imaging is only necessary if there are signs of pulmonary callus or metastases [10].

Since small cell neuroendocrine carcinomas of the cervix are rare, there are no randomized studies evaluating their treatment. The only two prospective series total 33 patients and do not allow a definitive conclusion to be drawn. Therefore, their treatment is modelled on that of other cervical tumours, while taking into account the characteristics and experience of pulmonary neuroendocrine tumours. In the case of localized tumors (stage I-IIA), it became apparent very early on that despite local treatment of the primary tumor, the majority of patients develop metastases, the main cause of death within three years.

Two authors have reported disappointing results of local treatment alone (surgery with or without radiotherapy) for localized tumors: Sheets et al. reported a three-year overall survival rate of 16% and a five-year progression-free survival rate of 0% [7]. Sevin et al. reported a progression-free survival rate at five years of 36% [3]. Mainly hematogenous (67-90% of cases) and lymph node relapses (34% of cases), a high incidence of lymphadenopathy at diagnosis (40-60%), and frequent vascular invasion were factors that prompted the majority of authors to combine systemic treatment with local treatment [9]. Three studies retrospectively compared local treatment alone (surgery) and local treatment combined with adjuvant chemotherapy. Thus, Zivanovic et al. found a rate of

The three-year recurrence-free survival rate of 83% for patients receiving cisplatin and etoposide chemotherapy versus 0% for local treatment alone [8]. Because of the rate of early metastatic dissemination, some authors have preferred to use neoadjuvant chemotherapy.

The role of chemotherapy appears to be established, but the sequence and type of chemotherapy is less established. The different regimens used in retrospective studies are very heterogeneous and extrapolated from lung cancer series. The combination of etoposide and cisplatin has proven to be superior in pulmonary neuroendocrine carcinomas and is now preferred over other chemotherapies. For localized tumors, the preferred local treatment is extended colpohysterectomy with bilateral adnexectomy with or without radiotherapy.

By combining surgery, radiotherapy and chemotherapy, Chan et al. were able to achieve a five-year survival rate of 32%, which is significantly higher than those reported in the different series. Long-term survivors were patients with tumors less than 2 cm in size who had undergone radical surgery.

For locally advanced tumors (stages IIb-IV) and inoperable patients, a combination of radiotherapy and chemotherapy is recommended, following the protocol of Hoskins et al [10].

In cases of metastatic disease or recurrence, chemotherapy with either cisplatin and etoposide alone or in alternation with VAC chemotherapy (vincristine, adriamycin and cyclophosphamide) is indicated [10].

Conclusion

Small cell neuroendocrine 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. Cervical CPC has a poor prognosis because it is remarkably resistant to various conventional therapies and lymph node and distant metastases are frequent and early.

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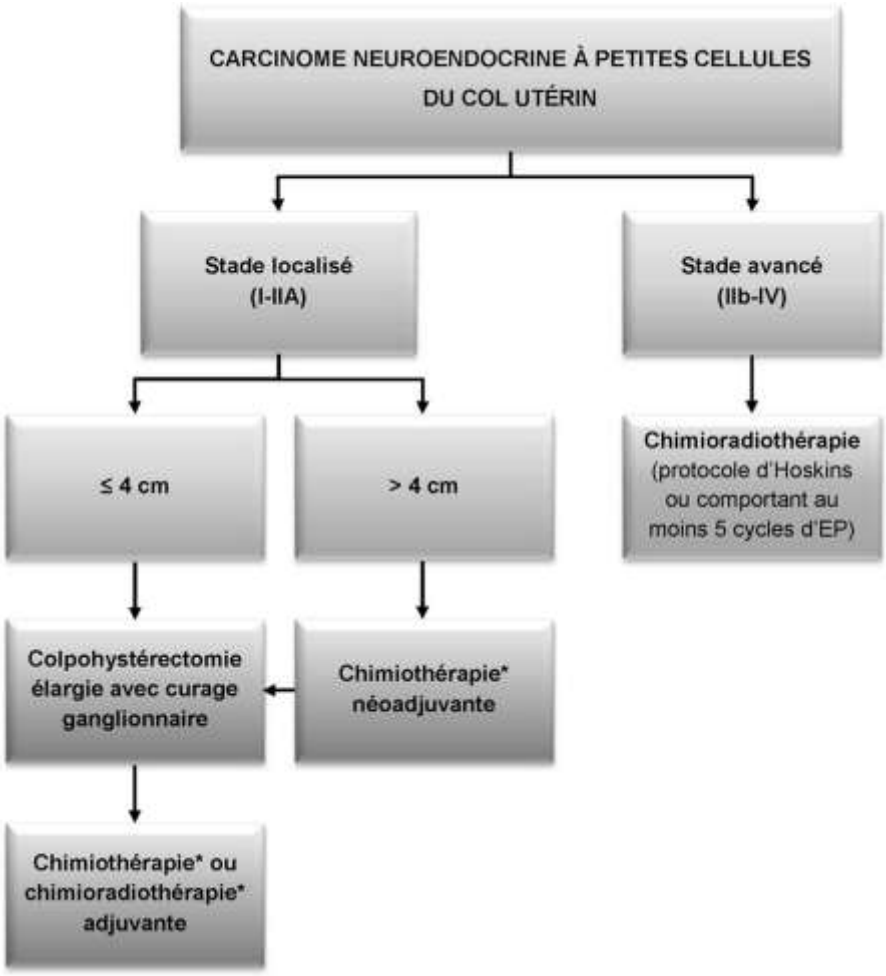
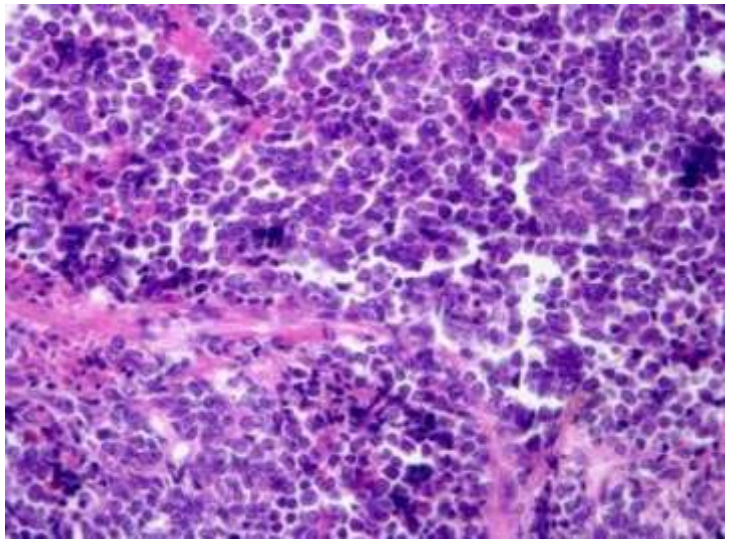


Therapeutic algorithm for the management of small cell neuroendocrine tumours of the uterine cervix.



Prolifération tumorale peu différencié compatible avec un carcinome à petites cellules du col utérin