Treatment policy of neuroendocrine small cell cancer of the cervix

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Summary

Small cell cancers of the cervix are very rare and aggressive tumours. It is difficult to manage these tumours. They are often diagnosed in an advanced stage and their prognosis is generally poor. There are no clinical trials, due to their rarity, that would suggest optimal treatment. The present report describes a patient with a neuroendocrine small cell cancer of the cervix Stage IB2 with a positive lymph node. The treatment consisted of radical hysterectomy and node dissection, adjuvant chemotherapy, chemoradiation and brachytherapy. Currently, after 52 months, the patient is well and free of disease. Since 1996, there has been a classification for neuroendocrine tumours (NETs) of the cervix in four categories (large cell, small cell, typical carcinoid and atypical carcinoid). The aggressive behaviour of neuroendocrine small cell cancer is demonstrated by the high percentage of early lymphatic node and vessel invasion (68 and 90%). Almost half of the patients with Stage I and II will recur with an estimated 5-year survival from 14% to a maximum of 55%. Multimodal therapy for these tumours appears to give good response but often implies severe side-effects.

Key words: Small cell; Cancer; Cervix; Neuroendocrine; Tumour; Multimodal treatment; Radical surgery; Chemoradiation.

Introduction

Neuroendocrine small cell cancer of the cervix (NSCCC) is a very rare entity. It accounts for about 0.5-6% of all cervical cancers [1-6]. Wentz and Reagan first described NSCCC in 1959 [7]. Since then only about 200 cases have been reported. The literature often denotes it as one of the most aggressive tumours of the female genital tract with a poor prognosis. A recent study showed that not only advanced stage but also smoking is considered as an independent poor prognostic factor [8]. It is difficult to manage and treat these tumours because of their very aggressive behaviour. There is often early vessel and lymphatic invasion, and early lymph node involvement. The tumour has a high recurrence rate and there are frequently early distant metastases [9-11]. Diagnosis is often made when the tumour is already in an advanced stadium, making surgery insufficient in most cases. There is a whole range of possibilities of adjuvant therapy but due to the rareness of NSCCC, it is impossible to have proper clinical trials that could establish the ideal treatment.

Case Report

The patient was a 43-year-old woman, G2P2A0. Her medical background included laparoscopic sterilization, tonsillectomy, and a penicillin allergy. The latest Pap smear, which was taken about two years ago, was normal.

She consulted her gynaecologist for intermenstrual and post-coïtal bleeding. Under speculum, a lesion was seen in the upper and lower lip of the cervix. The vaginal wall was normal. Bimanual examination of the parametria revealed no involvement. A biopsy taken from the cervix showed an undifferentiated small cell tumour of the cervix. Immunohistochemical staining was performed with a cytokeratin cocktail, leukocyte common antigen (LCA, CD45), chromogranine A, epithelial membrane antigen (EMA) and neuron-specific enolase (NSE). Only NSE and EMA were positive. The tumour of the cervix was staged as a stadium IB2 according to the FIGO classification.

Her treatment started with a radical hysterectomy and pelvic and para-aortal lymph node dissection. Postoperatively her hospitalization was complicated with an abdominal lymphocoele, which was quite painful and made relaparotomy necessary. Pathological examination showed that the tumour was 4.5 cm in diameter. It invaded all quarters of the cervix except between 9 and 12 o' clock, invading the outer third of the cervical thickness. Proximally it reached the uterine isthmus. There was extensive invasion in the vessels and lymphatic veins. However, the surgical section margins were all free of tumour. The cervix was ulcerated; tumour cells were small, arranged in sheets with irregular nuclei and a high nuclear/cytoplasm ratio. Mitotic figures were numerous. There were also several areas of necrosis.

Immunohistohemical staining showed that NSE and EMA were positive like in the biopsy but also positive for synaptophysin in some tumour cells (Figures 1-4).

One of the 37 lymph nodes was affected by tumour however without capsular invasion. The lymph node was located in the left fossa obturatoria.

The patient received four cycles of adjuvant VIP chemotherapy (etoposide, ifosfomide and cisplatin). Her fourth cycle of VIP had to be postponed because of leucopenia and trombopenia. She had some mild side-effects like nausea, vomiting, diarrhoea, and alopecia. She could not stand alizapride or metoclopramide.

Three weeks later, she received adjuvant chemo-radiation, which consisted of 50.4 Gy of four-field brick technique radiation and cisplatin (40 mg/m^2). After the chemoradiation brachytherapy of 10 Gy was given. She presented approximately a year later with symptoms of subileus, which was treated conservatively. Nevertheless, a few months later, she needed a side-to-side anastomosis because of obstruction of the small bowel.

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Fig. 1

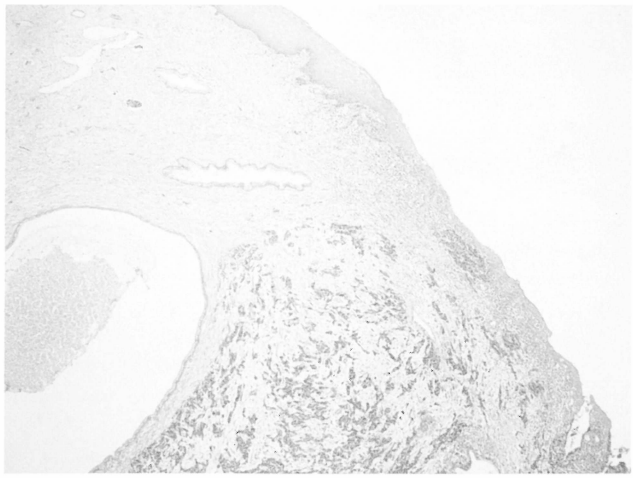

Fig. 2

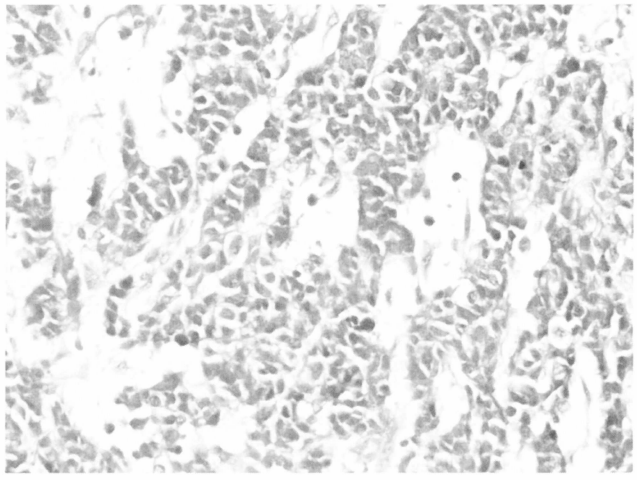

Fig. 3

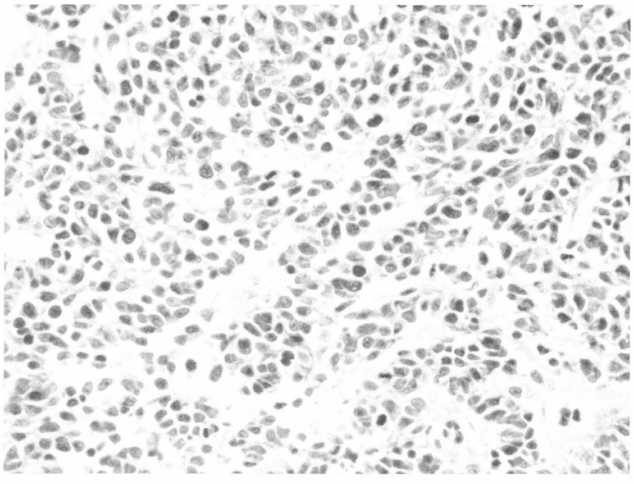

Fig. 4

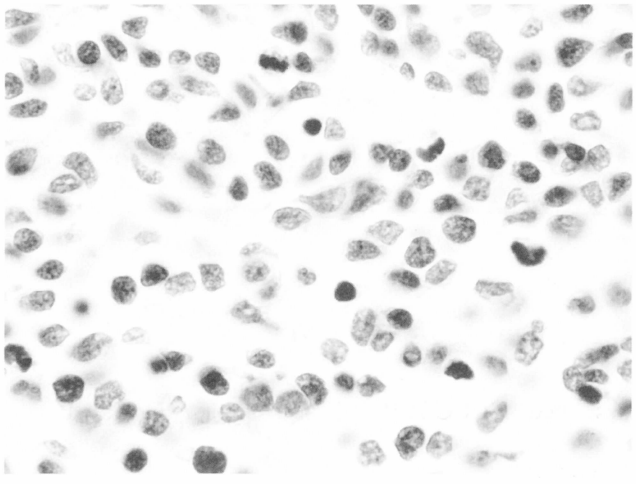

Figure 1. — HE staining.
Figure 2. — HE staining.
Figure 4. — Synaptophysin staining.
Figure 3. — NSE staining.

During that period she also had diarrhoea caused by radio-enteritis and urgency-incontinence that was caused by bladder radiation. Her miction problems were resolved with pelvic muscle training. A month later she also presented with an entero-vaginal fistula, which was first treated with octreotidum and TPN. After receiving parental nutrition, she developed jaundice with biochemical disorders of liver parameters. It was feared that she suffered from metastasic liver disease. A CT-scan of the upper abdomen showed a very small lesion, more likely to be a hemangioma, but metastasis could not be ruled out at that moment. Her jaundice disappeared and her liver tests normalised after the entero-vaginal fistula was surgically resolved and she started eating per os. Therefore, her problem of jaundice was likely caused by the TPN and octreotidum and was not due to metastasis. Now 52 months later, she is well and free of disease.

Discussion

About 240 cases of neuroendocrine tumours (NETs) of the cervix have been reported. A survey of 18 series of reports and studies (Table 1) showed that the mean age of patients with NETs of the cervix was about 46.8 years (range 22-92 years) with 47% of the patients already in Stage II, III or IV during diagnosis.

The literature in the past used many terms to describe this aggressive class of morphologically varied tumours.

Table 1. — *Reported cases of NETs of the cervix.*

Year	Author	n	mean age
1981	Pazdur *et al.* [12]	4	49
1987	Barrett *et al.* [13]	7	48
1988	Sheets *et al.* [9]	14	45
1988	Van Nagell *et al.* [10]	25	49
1989	Silva *et al.* [14]	38	53
1990	Tabbara *et al.* [15]	3	44
1991	Miller *et al.* [16]	14	48
1991	O'Hanlan *et al.* [17]	2	51
1992	Morris *et al.* [18]	10	37
1993	Lewandowski *et al.* [19]	4	40
1994	Abeler *et al.* [10]	26	45
1995	Hoskins *et al.* [20]	11	47
1997	Lim *et al.* [21]	1	37
1999	Collinet *et al.* [22]	5	53
2000	Appetecchia *et al.* [23]	1	54
2001	Straughn *et al.* [24]	16	38
2002	Conner *et al.* [25]	23	43
2003	Chan [8]	34	42

Examples of other terms used for small cell neuroendocrine tumours are carcinoid small cell carcinoma, agyrophil cell carcinoma (apudomas), small cell tumour with neuroepithelial features, oat cell carcinoma, small cell undifferentiated carcinoma, squamous cell carcinoma of the small cell type, small cell carcinoma with squamous cell, small cell carcinoma with adenocarcinomatous differentiation [1, 10-11]. Because of the different terms used to describe the tumour there is not only confusion, but also underestimation of its frequency. As mentioned before, it accounts for about 0.5-6% of all cervix carcinomas.

To obtain a uniform terminology, in 1996 the College of American Pathologists and the National Cancer Institute adopted a new classification system (Table 2) [1]. NETs were classified into four categories similar to the classification of tumours of the lung. NSCCC has a biological behaviour similar to that of small cell carcinoma of the lung.

Table 2. — *Classification of neuroendocrine tumours of the cervix. 1996 - the College of American Pathologists and the National Cancer Institute [1].*

	Cytological features	Mitosis	Necrosis
Typical carcinoid	No cytological atypia	Rare	None
Atypical Carcinoid	Cytological atypia	=/< 10 MF /HPF*	Focal
Large cell neuroendocrine carcinoma	Large cells with vesicular nuclei and prominent nucleoli	> 10 MF / HPF*	Geographic
Small cell neuroendocrine carcinoma	Small round cells with minimal cytoplasm	Abundant	Extensive

*Mitosis frequency/High power field.

The panel described histological criteria for small cell carcinoma of the cervix: small, round cells in solid sheets, scant cytoplasm, hyperchromatic nuclei, absent nucleoli, numerous mitotic figures and extensive necrosis.

It is often difficult to distinguish this tumour from other undifferentiated tumours, but electron microscopy or immunohistochemical staining can help to make or to confirm the diagnosis [26]. The diagnosis of small cell carcinoma remains a morphologic diagnosis, not an immunohistochemical one. These tumours do not always express neuroendocrine markers [1, 25], though stainings for chromogranin A, neuron-specific enolase or synaptophysin are useful.

HPV is associated with the pathogenesis of this neoplasm. Wistuba et al. studied the presence of human papillomavirus sequences in the neuroendocrine tumour cell, 53% were positive for high-risk HPV sequences, type 16 and 18 [27]. In contrast to squamous cell carcinoma of the cervix, where HPV 16 is two to four times more frequent than HPV18, Wistuba found that especially HPV18 is more associated with neuroendocrine tumours of the cervix, being five times more frequently found than HPV16 [27]. HPV infection and smoking may have a synergistic effect on the pathogenesis of cervical neoplasms [8, 28]. Recent multivariate analysis evaluating prognostic factors in NSCCC by Chan et al. showed that smoking was a significant poor prognostic factor for survival in early stages. Age, race, menopause status and hormone replacement therapy were not found to be important prognostic factors [8].

Neuroendocrine tumours can cause systemic manifestations and clinical symptoms due to ectopic hormone production, as seen in NETs of the gastrointestinal tract, head and neck, and pancreas [29]. However, NETs of the cervix that cause endocrine manifestations are extremely rare, although some cases have been reported. Those cases include carcinoid syndrome, Cushing's syndrome and hypoglycaemia [30-32]. Abeler *et al.* and Silva *et al.* suggested that these tumours produce hormonal polypeptides in an inactive form or in insufficient amounts to produce symptoms [11, 14]. Other more rare clinical presentations of this tumour entity have been described such as Eaton-Lambert syndrome or a compression of the spinal cord and cauda equina due to metastatic deposits [33, 34].

Most cases described by Chan presented with vaginal bleeding [8]. According to Straughn *et al.* most patients with NSCCC (88%) presented with symptoms of abnormal bleeding or postcoïtal spotting [24]. The other 12% of the patients presented with vaginal discharge or a pelvic mass. In their study no cases were discovered on routine Papanicolaou smear. Ciesla *et al.* also stated that there was little room for conventional cervicovaginal smears in diagnosis of small cell cancer of the cervix [26]. This may point to the importance of doing a colposcopic examination in case of vaginal bleeding i.e., given the higher sensitivity of colposcopy as compared to cytology. In our opinion, due to its fast development there is little room for cytology in the pre-clinical stage. As mentioned before 47% of neuroendocrine small cell cancers are diagnosed in Stage II, III or IV while almost none are diagnosed with pap smears.

The tumour has a very aggressive behaviour and poor prognosis. Five-year survival ranges from 14% to 55% [10, 11]. A more recent series showed a five-year survival of 31.6% in early stage disease [8].

Authors describe it as the most aggressive tumour of the female genital tract. It is often compared to small cell carcinoma of the lung, where prognosis and early metastasis is also known. It has early lymphovasvular space invasion, 68% [8], while Abeler *et al.* described 90% vessel invasion [11]. Some authors reported 57-68% lymph node invasion present at diagnosis [8, 9]. The tumour has a high tendency of recurrence. Van Nagell *et al.* reported 47% recurrent disease in Stages I and II [9]. Compared to large cell tumours and squamous cell tumours the recurrence rate is higher especially in early stages.

It is not clear what the best treatment is, although some cases that were successfully treated with surgery alone have been reported [24], it seems clear that more aggressive therapy is needed due to the early spread even if there are severe side-effects as in our case report. For example, Sheets *et al.* treated patients with early stage small cell tumours of the cervix with surgery and only pelvic irradiation in those with nodal metastasis [9]. Twelve out of 14 patients died of disease within eight to 31 months after diagnosis. Most reported carcinomas in

an early stage in the literature were treated by radical hysterectomy and radiation therapy with or without adjuvant chemotherapy (Table 3).

Because the tumour bears much similarity to small cell cancer of the lung and a combination of cisplatin, etoposide and cyclophosphamide has proved to be useful in small cell cancer of the lung, some authors have suggested that similar adjuvant chemotherapy should be given in this type of tumour of the cervix [12, 15, 17, 21]. Several authors obtained complete remission with this multimodal approach. According to Chang *et al.* and Boruta *et al.*, regimens containing VAC (vincristine, doxorubicine and cyclophosphamide) or PE (cisplatin, etoposide) have an improved survival for patients with adjuvant chemotherapy or chemoradiation in early stage disease [8, 35]. O' Hanlan *et al.* reported two successfully treated cases [17]. They treated two patients with chemoradiation after surgery. Chemoradiation consisted of pelvic radiation and cisplatin/cyclophosphamide/etoposide in one patient and pelvic radiation with cisplatine/etoposide in another. Severe myelosuppression and persistent neuropathy were seen in both patients because of this approach.

Kim *et al.* reported a case with regional nodal spread in 1996 that was successfully treated with surgery, radiation and adjuvant chemotherapy with a follow up of 92 months [36]. The authors claimed it was the first reported case of long-term survival of a patient with regional nodal spread. A year later Lim *et al.* reported a similar case successfully treated with bilateral involving nodes of the obturator, common and external nodes with a follow-up of 54 months [21]. Lim *et als'*. treatment policy consisted of surgery, chemotherapy (etoposide/cisplatin) and pelvic radiation. They did not consider concurrent chemotherapy and pelvic radiation because of severe myelosuppression and neuropathy. It was believed chemoradiation could compromise effectiveness due to difficult chemotherapy dosage and difficult scheduling of treatment. A recent report by Chan *et al.* provided a management scheme for neuroendocrine cervical carcinoma suggesting that neoadjuvant chemotherapy be considered in lesions greater than

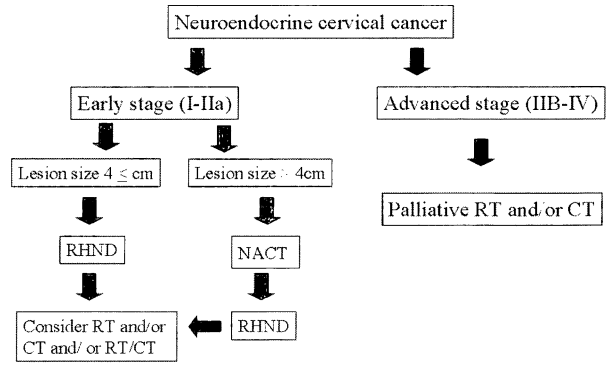

Figure 5. — Modified management scheme for neuroendocrine cervical carcinoma.
RT: radiotherapy; CT: chemotherapy; RT/CT: concurrent chemotherapy; RHND: radical hysterectomy with node dissection; NACT: neodadjuvant chemotherapy.

4 cm to reduce tumour size before surgery [8].

In our case a combination multimodal approach was also chosen, as described above in our current report. After surgery our patient was treated with adjuvant chemotherapy, which is similar to the chemotherapy treatment small cell cancer of the lung. In addition to that, after adjuvant chemotherapy, our patient was also treated with concurrent chemoradiation, even if there were risks of severe side-effects. With a recurrence rate of 47% in Stages I and II, we think aggressive therapy is justified. A modified management scheme of Chan *et al.* [8] has been proposed by adding concurrent chemoradiation (Figure 5). It has to be underscored that due to the rarity of the disease, experience with adjuvant chemotherapy, radiotherapy or concomitant chemoradiation is limited.

Conclusion

Neuroendocrine small cell cancer of the cervix is a rare but aggressive tumour, often diagnosed in an advanced stage while pap smears do not contribute much to its early detection.

Table 3. — *Some other reported possibilities of treating Stage IB small cell carcinoma of the cervix reported in the literature.*

Year	Author	Stage	Treatment policy	Outcome
1987	Barret [12]	IB1	S + RT	DOD 11 months
1991	O'Hanlan [16]	2 x IB	S + RT/CT	NED 28,47 months
1994	Abeler [10]	2 x IB	RT	2 x recurrent disease
1995	Sheets [8]	12 IB	4 x S	12 patients DOD after 8 to 31 months
		and 2 IIA	8 x S + RT (if nodal metastasis)	
1996	Appetechia [22]	IB1	S + RT	NED 20 months
1996	Kim [35]	IB	S + RT + CT	NED 92 months
1997	Lim [20]	IB2	S + CT + RT	NED 54 months
2000	Collinet [21]	IB	S + RT	NED 26 months
2001	Straughn [23]	2 x IB	S + RT	DOD 40 months/NED 264 Months
		5 x IB	S + RT + CT	DOD 14, 15, 19 months; AWD 19 months; NED 16 months
		2 x IB	S + CT	DOD 9, 54 months
		IB	CT + RT	DOD 22 months
		IB	S	NED 60 months
2004	Present report	IB2	S + CT + RT/CT	NED 52 months

S: Surgery; CT: chemotherapy; RT: radiotherapy; DOD: Dead of disease; NED No evidence of disease; AWD: Alive with disease. RT/CT concurrent chemoradiation.

After a review of the literature, most authors reach the same conclusion: because of the rarity of the disease, there is a lack of clinical trials that can give evidence for the must optimal treatment. A survey of multiple studies and case reports in the past could be useful, but due to the many terms used for small cell carcinoma of the cervix it is difficult to do a proper meta-analysis.

Even if such a study were done, with small series and a high diversity in ways of treatment, it does not seem possible to make evidence-based meaningful conclusions. Even though there is little information in the literature about the optimal treatment, mortality rates and high recurrence behaviour indicate that multimodal therapy seems to be the best approach. Multimodal therapy must also be considered even in early stages.

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