Small Cell Neuroendocrine Cervical Carcinoma with 1-Year Follow-up: Case Report and Review

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Abstract. *Background: Small cell neuroendocrine cervical carcinoma (SCNCC) is a rare tumor that comprises 1-3% of cervical tumors. SCNCC exhibits clinical and biological characteristics of both cervical neoplasm (such as local aggressiveness and involvement of papillomavirus) and neuroendocrine small cell cancer of any site (such as early dissemination of the disease and loss of heterozygozity at different loci) making it an original nosologic entity. There is no unanimous opinion regarding the optimal management strategy. Case Report: A 48-year-old Caucasian woman, para 3, referred postmenopausal bleeding of 2 months' duration. Preoperative investigation diagnosed an infiltrating squamous carcinoma of the cervix. A radical hysterectomy with bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy were performed. Final diagnosis was SCNCC (FIGO stage III B) and therefore adjuvant radiochemotherapy was given. At 1-year follow-up the patient was free of disease. Conclusion: Despite the retrospective studies and case reports reported, in literature the best modality of treatment remains controversial. Multicenter clinical trials are needed to determine a univocal and effective treatment for SCNCC in order to achieve significant survival benefit.*

Small cell neuroendocrine cervical carcinoma (SCNCC) is a rare tumor that comprises 1-3% of cervical tumors (1, 2). Reagan *et al.* (3) first described small cell undifferentiated (neuroendocrine) carcinoma of the uterine cervix in 1957, distinguishing it as a separate entity from what had previously been thought to be a rare subtype of squamous cell carcinoma. SCNCC exhibits clinical and biological characteristics of both cervical neoplasm (4) (such as local aggressiveness and involvement of papillomavirus) and neuroendocrine small cell cancer of any site (such as early dissemination of the disease and loss of heterozygozity at different loci) making it an original nosologic entity.

Histopathologically, SCNCC resembles small cell carcinoma of the lung and is classified as small cell carcinoma of the cervix in the World Health Organization International Histologic Classification of Tumors (5). It is noted for its very aggressive behaviour and has the poorest prognosis of the various cervical carcinomas, even after multimodal therapy (6). Even if its natural history is well known, its extreme rarity represents a limitation in the understanding of both management and effective therapy. Here, the case of a 48-year-old Caucasian woman with a polypoid SCNCC, initially misdiagnosed as infiltrating squamous carcinoma of the cervix, and the management strategies adopted are described.

Case Report

Clinical history. A 48-year-old Caucasian woman, para 3, referred postmenopausal bleeding of 2 months' duration. Gynecological examination and transvaginal echography showed an endocervical mass. Colposcopy and hysteroscopy confirmed the polypoid mass arising from the endocervical side of the posterior lip of the cervix (Figure 1). Biopsy of this tumor was reported histologically as infiltrating squamous carcinoma of the cervix. Laboratory findings and tumors markers [CA125, CA19-9, CA15-3, tissue polypeptide-specific antigen (TPS) and carcinoembryonic antigen (CEA)] were within normal range.

Magnetic resonance imaging (MRI) of the abdomen and pelvis revealed lymph node enlargement 1×1.5 cm and

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2.5×1.5 cm right and left side respectively. She had radical hysterectomy with bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy. Histological examination revealed an endocervical necrotic area infiltrating for 2 mm, and 5 lymph nodes were metastasized.

The tumor on both the revised biopsy and the specimen was composed of masses, cords and trabeculae of small cells, with oval to spindle-shaped hyperchromatic nuclei, and a high mitotic rate (>2 mitoses × high power field). Nuclear molding was often observed and nuclear detail was fairly frequently obscured by smudging artifact. Cytoplasm was scanty (Figures 2 and 3). No areas of squamous or adenocarcinoma were identified and there was no *in situ* component. The immunocytochemical profile demonstrated marker positivity for neurone-specific enolase (NSE) and synaptophysin (Figure 4). An undermining intact cervical columnar epithelium was seen. Final diagnosis was SCNCC (International Federation of Gynecologists and Obstetricians; FIGO, stage III B). The patient received adjuvant radiochemotherapy consisting of 6 cycles of cisplatin and paclitaxel. At 1-year follow-up the patient was free of disease.

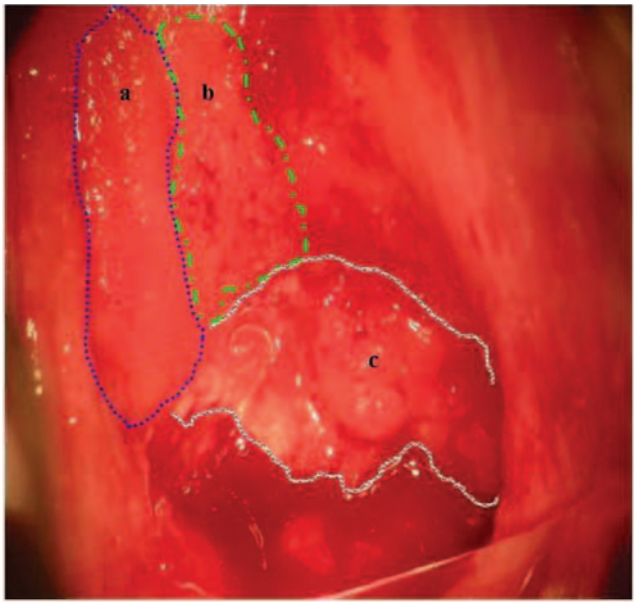

Figure 1. *Colposcopy: polypoid mass arising from the endocervical side of the posterior lip of the cervix: a: Punctuation pattern; b: mosaic pattern; c: suspect polypoid mass.*

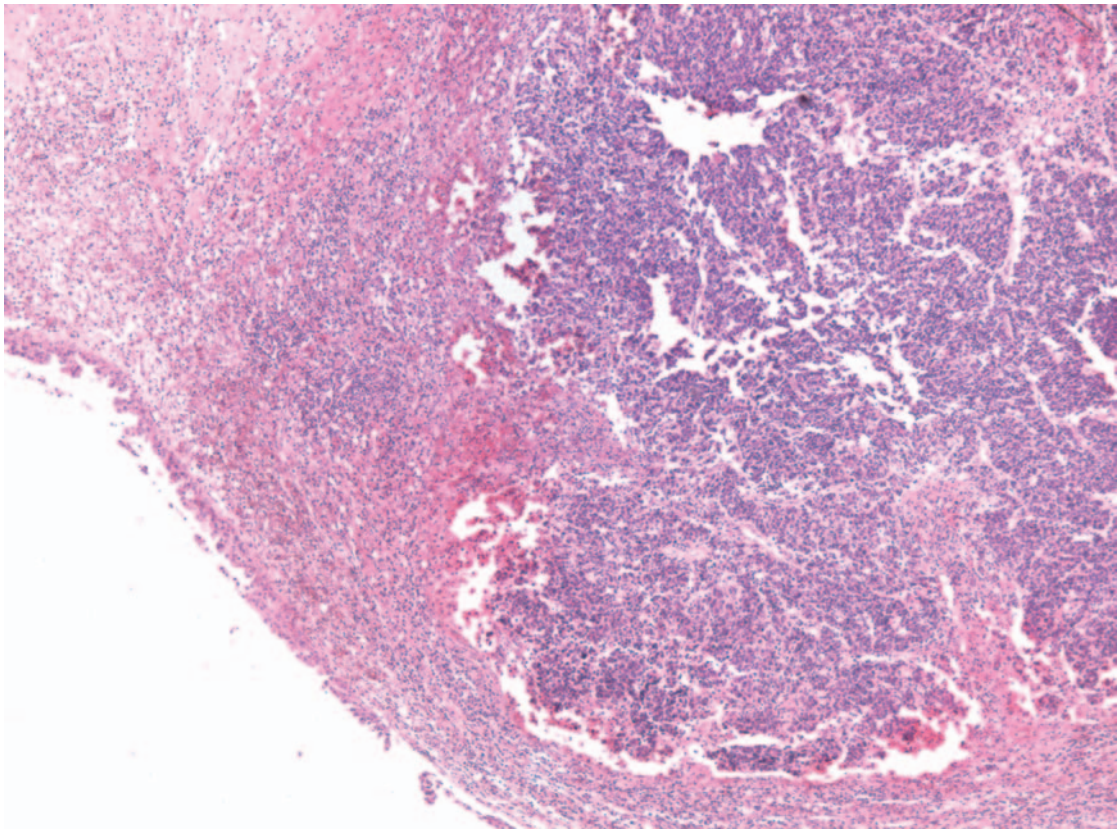

Figure 2. *The tumor showing proliferation of the neoplastic cells in the subepithelial area (hematoxylin and eosin ×106).*

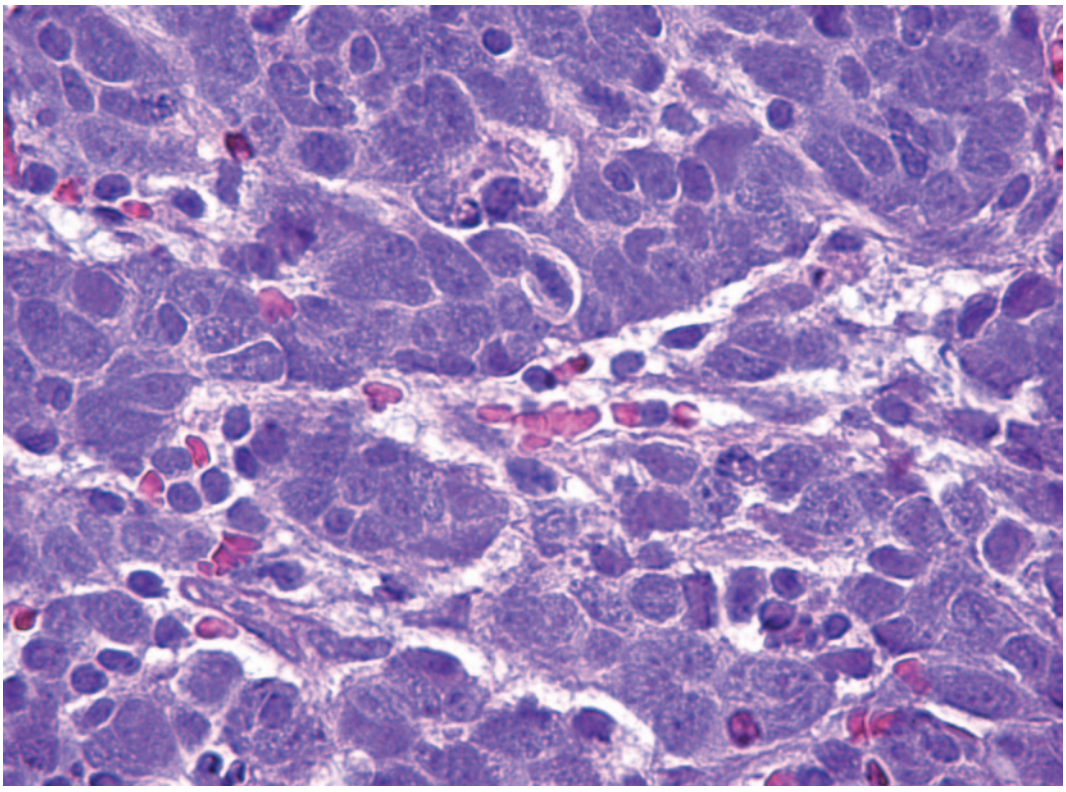

Figure 3. *High power image showing malignant cells with hyperchromatic nuclei arranged in sheets and broad trabeculae (hematoxylin and eosin ×630).*

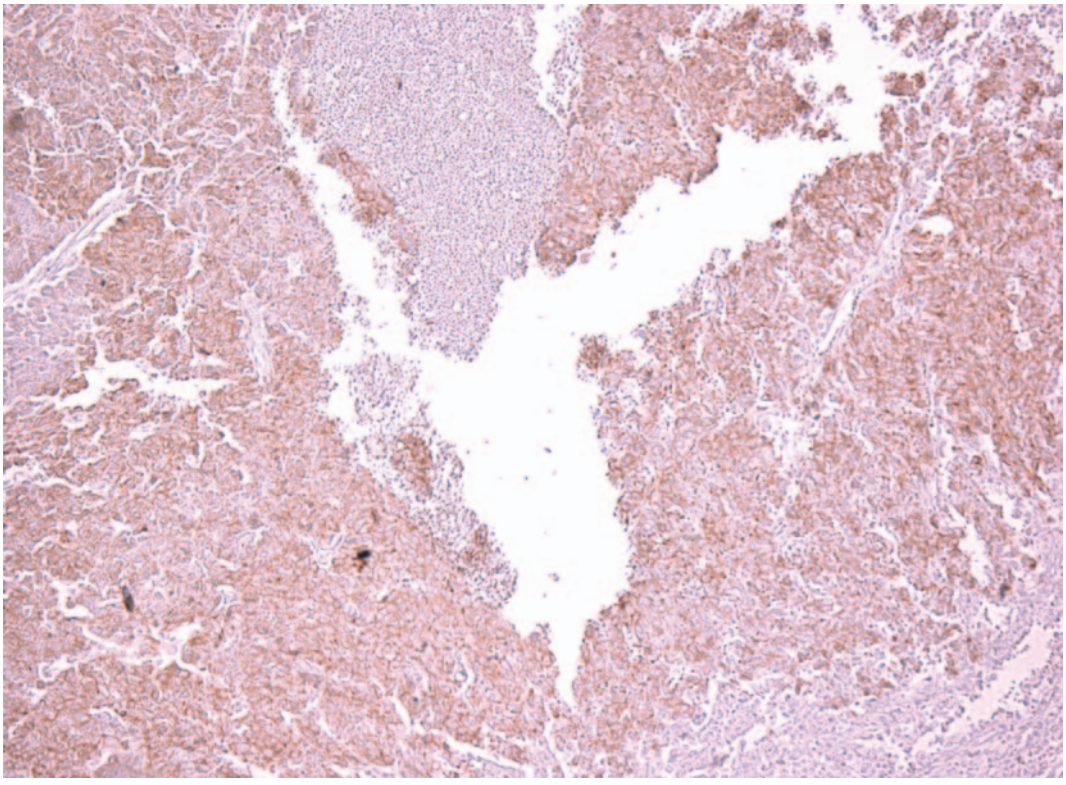

Figure 4. *IHC stains. Tumor cells with diffuse, strong staining for synaptophysin (immunoperoxydase ×200).*

Table I. *Characteristics of the patients with small cell neuroendocrine cervical carcinoma reported in the literature.*

	Number of cases	Median Age (years)	FIGO stage (number of patients)	Treatment (number of patients)	Follow-up (number of patients)
Albores Saavedra *et al.* (2008) (9)	31	–	—	–	2-year OS 50%
	5	43	IA (2)	RH (1), RH+CT (1)	NED (5)
			IB (2), IC (1)	RH+CT (3),	
Pazdur *et al.* (1981) (29)	4	49	II (2), IIIB (1), IVB (1)	RT+CT (2), RH+RT+CT (1), CT (1)	4DOD
Silva *et al.* (1989) (10)	9	–	IB (5), IIB (4), IIIB (1), IV (1)	RH+RT or only RT	11% AW, 87,5% DOD
	38	53	I (17), II (4), III (11), IV (6)	—	25 DOD, 8 NED
Barrett *et al.* (1987) (30)	7	48	IB (4)	RH (2), CT (1), refused (1)	2DOD, 1 NED, 1 LOST
			IIIB (1)	RH	1 DOD
			IVB (2)	RT	1 DOD
Gersell *et al.* (1988) (31)	15	42	IB (9), IIA (1), IIB (2), IIIB (2), IV (1)	—	3AW, 10 DOD
Walker *et al.* (1988) (32)	14	–	I (4), II (5), III (2), IV (3)	RH+RT (1), RH+CT (2), RT+CT (1), CT (1), RT (9)	1 NED, 1AWD, 11 DOD
Van Nagell *et al.* (1988) (1)	25	49	IB (12), IIA (3), IIB (2), IIIB (4), IV (4)	RH+RT, RT	70% DOD
Sheets *et al.* (1988) (24)	14	45	IB (12), IIA (2)	RH+RT (8), RH (5), RH+CT (1)	13 DOD, 1 NED
Tabbara *et al.* (1990) (33)	3	44	IB (1), IIB (1), IVB (1)	CT+RH (1), CT+RT (1), CT (1)	2 NED, 1 AWD
Miller *et al.* (1991) (34)	14	48	I (6), II (3), III (2), IV (3)	RT (6), RH+RT+CT (4), CT (3), refused (1)	7 DOD, 6 NED, 1 LOST
O'Hanlan (1991) (35)	2	41 and 62	IB (2)	RH+CT+RT (2)	2 NED
Morris *et al.* (1992) (36)	10	37	IB (7), IIA (1), IIB (2)	RH+CT (2), RH+RT+CT (1), RT+CT (1), CT+RT (6)	4 NED, 5 DOD, 1 AWD
Lewandoski *et al.* (1993) (28)	4	40	IB (1), IIA (1), IIB (1), IVB (1)	RH+CT (1), RH+CT+RT (1), CT+RH+CT+RT (1), CT+RH+CT (1)	3 NED, 1 DOD
Abeler *et al.* (1994) (14)	26	45	IA (2), IB (13), IIA (1)	RH (10), RT+RH (4) or RT (2) alone	3 NED, 3 AW, 2 AWR
			IB (2), IIB (6), III (2)	RT alone	3 DOD, 5 AWR
			IV (3)	RT (1), CT (1), RT+CT (1)	3 DOD
Hoskins *et al.* (1995) (37)	11	47	IB (3)	RH+RT+CT	1 three-year OS, 2 DOD
			IA (1)	RT+CT	DOD
			Incidentally diagnosed (2)	RH (2)	1 three-year OS
			IIIB (4)	RT+CT	DOD
			IVB (1)	RT+CT	DOD
Perrin and Ward (1995) (38)	5	–	IB-IIA	RH+-CT	DOD 4, NED 1
Sykes *et al.* (1999) (39)	11	40	–	RH+-RT+-CT	3 NED
Sheridan *et al.* (1996) (40)	5	37	–	CT+RH (1) CT+RT (1), RT+CT (1), RH+RT+CT (2)	5DOD
Sevin *et al.* (1996) (2)	12	45	–	–	5 year AW 36 % , 7 DOD
Mannion *et al.* (1998) (41)	38	48	–	–	2 NED
Chang *et al.* (1998) (26)	23	43	IB (19)	RH+CT (20), RH+CT+RT (3)	13 NED, 10DOD
			IIA (3), IIB (1)		
Wang *et al.* (1998) (42)	7	45	–	–	6 DOD
Lim FK *et al.* (1999) (43)	1	37	IB2	RH+CT+RT	AW
Delaloge *et al.* (2000) (4)	10	33	IA (1)	CT+BT+RH	DOD
			IB (5)	RH (1), RT+BT+RH+CT (1), BT+RH+CT (1), CT+RT (1), CT+RT+RH (1)	DOD, DOD, AW, DOD, AW
			IIB (1)	RT+BT	DOD
			IIIB (1)	RT+RH+BT	DOD
			IVA (2)	BT+RH+RT (1), RH alone (1)	DOD
Collinet *et al.* (2000) (45)	5	53	IB (1)	SH+RT	NED
			IIA (1)	RH+CT	NED
			IIB (1), IVA (1)	RT	NED, DOD
			IIIB (1)	RH+RT+CT	DOD

Table I. *continued*

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	Number cases	Median Age (years)	FIGO stage (number of patients)	Treatment (number of patients)	Follow-up (number of patients)
Boruta et al. (2001) (11)	11	39	IB (9), IIA (2)	RH+CT (4), RH+CT+RT (7)	8 DOD, 3 AW
Straughn *et al*. (2001) (12)	16	38	IB (11)	RH (1), RH+RT (2), RH+RT+CT (5), RH+CT (2), RT+CT (1)	7 DOD, 3 NED, 1 AWD
			IIB (4)	CT (1), CT+RT (1), RT (1),RT+CT (1)	3 DOD, 1 NED
			IV (1)	CT	DOD
Conner *et al*. (2002) (45)	23	43	IB-IIB	RH (7), +RT (2) or RT+CT (3), RT alone (2) +CT (3), RH+RT (6)	15 DOD, 7 AW
Viswanathan *et al*. (2004) (6)	21	46	IB (15)	RH (2), RH+CT (4), RT (3), RT+CT (6)	6 AW, 9 DOD
			IIA/B (3), IIIB (3)	RT (6)+CT (3)	9 DOD
Weed *et al*. (2003) (46)	15	39	IA (1)	RH	DOD
			IB (4)	RH+RT+CT	AW1
			IIA (1)	RH+RT	DOD
			IIB (2), III (1)	RT+CT	DOD
			IV (6)	CT (2), RT+CT (3), S+RT+CT (1)	DOD
Chan *et al*. (2003) (16)	34	42	IB (20), IIA (3)	RH (17), SH (6)+postoperative	13 NED
			IB (1), IIA (1), IIB (2), III (5), IV (2)	RT (11), CT (1), RT+CT (3) RT (4), CT (6), 1 refused	9 DOD
Wang *et al*. (2004) (18)	22	38	IB (16), IA (2), IIIB (1), IIIA (3)	–	–
Ishida *et al*. (2004) (47)	10	–	IA2-IIB	–	median survival 2.5 years
Tangjitgamol *et al*. (2005) (19)	24	47	IB (8), IA (1)	RH (2), RH+CT (2), RH+ RT (4), CT alone (1),	4 NED, 5 DOD
			IB (7), IIB (3), IIIB (5)	RT (8), RT+CT (7)	15 DOD
Tsunoda *et al*. (2005) (48)	11	46,3	IB (4)	RH (2), RH+CT (2),	2 AW, 8 DOD, 1 LOST
			IIB (3)	RH+RT (2), SH+CT (1)	
			IIIB (3)	RH+CT (1), RT+CT (2)	
			IVB (1)	RT+CT	
Wang *et al*. (2006) (27)	25	–	IA-IVB	S+–CT+–RT or RT+– CT	median survival 2 years
Kasamatsu *et al*. (2007) (5)	10	41	IB (8)	RH (4), RH+RT (3), RH+CT (1)	5 DOD, 3 NED,
			IIB (2)	RH (1), RH+CT (1)	DOD (1), AWD (1)
Gressner *et al*. (2007) (49)	1	67	IIB	RT	DOD
Lee *et al*. (2008) (17)	68	46	IB1 (43), IB2 (15), IIA (10)	RH (7), CT+RH (11), RH+CT (24), RH+CT +– RT (26)	5-year survival stage IB1 55% , IB2-IIA 32%
INDEX CASE (2008)	1	48	IIIB	RH+RT+CT	1 year NED

SH: Simple hysterectomy; NED: no evidence of disease; RH: radical hysterectomy; DOD: dead of disease; RT: radiation therapy; AW: alive, well; CT: chemotherapy; AWD: alive with disease; BT: brachytherapy; AWR: alive with recurrence; LOST: lost at follow-up.

Discussion

SCNCC is known to be highly malignant and is associated with the lowest rate of survival of cervical cancer even after multimodal therapy (7). Histopathologically, neuroendocrine cervical carcinoma resembles small cell carcinoma of the lung and is classified as small cell carcinoma of the cervix in the World Health Organization International Histologic Classification of Tumors. The overall 5-year survival rate for patients with SCNCC has been reported to range from 17% to 67% for all stages (8).

In a recent study, the 5-year survival rate of patients with FIGO stage IB1 disease was between 50% and 60% , which was significantly poorer than the 90% rate for patients with stage IB1 squamous cell carcinoma (6).

Considering the poor prognosis of SCNCC, more details about prognostic factors were investigated.

The clinical and pathological prognostic factors recognized to have poor prognosis are smoking status, polypoid pattern (9), presence of positive lymph nodes, pure histology, treatment with surgery, margin status (1, 4, 10-16) and advanced FIGO stage (12, 17). Immunohistochemical prognostic factors were also evaluated. Straughn *et al*. (12) investigated the relationship between molecular markers and survival. In their series, 14 (88%) out of 16 small cell carcinomas were positive for NSE, chromogranin, or synaptophysin. Patients whose tumors were positive for chromogranin had a significantly poorer survival rate than those whose tumors were chromogranin negative. The authors also found a trend towards poorer survival for patients whose

tumors did not express p53. However, they found no correlation between survival and expression of erbB2, proliferating cell nuclear antigen or c-myc included in the study for comparison. Among them, five (36%) exhibited a strong and diffuse staining pattern. Even if SCNCC is similar to small cell lung cancer, at immunohistochemical evaluation of SCNCC, overexpression of c-kit protein is an infrequent event in comparison with that in small cell lung cancer. This report may reflect the difference in etiopathogenetic mechanisms underlying these two types of small cell carcinomas (18).

Tangjitgamol *et al*. (19) studied immunohistochemical prognostic factors to reveal abnormalities in the expression of the growth factor receptors or enzymes involved in the neoplastic process and their possible role as prognostic indicators were determined to aid in the selection of new anticancer agents to improve treatment outcome. In this study, VEGF expression presented an high prevalence and HER-2/neu expression was significantly associated with survival. Moreover, patients with HER-2/neu-negative expression tumors had significantly shorter survival than those whose tumors were positive, of 14.2 months (95% CI, 10.6217.7 months) *versus* 33.1 months (95% CI, 0276.92 months) (p=0.03). There was a trend towards worse survival in patients with EGFR expression, but this finding was not significant. Finally, the combination of negative HER-2/neu expression and positive EGFR expression had the worst impact on survival. On the basis of these findings, clinical trials were proposed to investigate the therapeutic agents that target these proteins. This target therapy may be used singly, or in combination with other active chemotherapeutic drugs, or as a radiosensitizer. Given the high prevalence of VEGF expression, one might try to incorporate inhibitors of VEGF receptor in the treatment of neuroendocrine cervical carcinoma. Although these authors demonstrated a more favourable prognosis of patients with positive HER-2/neu expression tumors over those with negative expression, most of the patients in both groups had poor outcome. Tangjitgamol hypothesized that interferon can up-regulate the expression of HER-2/neu which might improve the prognosis of patients whose tumors do not express this marker. In patients whose tumors expressed HER-2/neu, trastuzumab (Herceptin™) treatment could also be combined with other chemotherapeutic drugs to maximize the potential therapeutic effects.

Due to the rarity of SCNCC, no multicenter study has been conducted on the disease and the optimal initial therapeutic approach has not been clarified. Several retrospective studies and case series are reported in the literature (Table I).

Although radical surgery is not associated with prolonged survival (20), most gynecological oncologists and patients favor radical surgery, which is the standard surgical procedure for stages IB to II cervical carcinoma of the ordinary type. In comparison, the prognosis for patients with cervical squamous cell carcinoma who are treated with radical hysterectomy is good. Recurrence develops in 10 to 15% of patients with stages IB or IIA disease who undergo radical hysterectomy, with or without postoperative radiation of the whole pelvis (21). Following radical hysterectomy, the difference in outcome among patients with squamous cell carcinoma and those with SCNCC may be due to differences in the biological behaviour of the carcinomas.

In patients with SCNCC, pelvic control alone does not usually lead to a good outcome because of the high incidence of distant metastasis in the early stage. The development of widespread hematogenous metastasis is the most important pattern in SCNCC, and controlling hematogenous spread should be a top priority in the attempt to improve the survival of patients with this type of cervical carcinoma.

On the contrary, morbidities associated with radical hysterectomy such as lymphedema or chronic bladder dysfunction (in 3% of patients), ureterovaginal or vesicovaginal fistula (in 1%-2%), lymphocele formation (in 5%), small bowel obstruction (in 1%), pulmonary embolism (in 1%-2%), injury to the obturator or genitofemoral nerve, and blood loss requiring transfusion (22) may interfere with systemic postoperative adjuvant therapy for the control of distant metastasis.

Recent studies (2, 5, 6) stated that pelvic control by radical hysterectomy does not appear to be generally beneficial for patients with SCNCC, and radical hysterectomy should be limited to those with an early invasive lesion without obvious lymph node metastasis. On the contrary, non-radical hysterectomy followed by new, aggressive adjuvant chemotherapy should be administered.

Thus, radical hysterectomy does not appear to be beneficial in patients with SCNCC and indications for this treatment should be limited.

In the presented case, radical surgery was performed because of the misdiagnosis as infiltrating squamous carcinoma of the cervix at cervical biopsy. Different schedules of chemo- and chemoradiotherapy were considered to treat SCNCC. The optimal treatment strategies for patients with early-stage disease have not yet been determined (6, 12, 17, 22).

Neoadjuvant chemotherapy has been recommended for patients with tumor size >4 cm (2, 12, 23) but although neoadjuvant chemotherapy might be useful for enhancing the resectability of bulky tumors, it did not improve survival. However, concurrent chemoradiation, especially primary combined chemoradiation, could be used to treat patients with advanced stage disease despite their poor prognosis as it might allow patients to do a little better (17). Favorable results have been reported for patients with SCNCC who received concurrent chemoradiation followed by several additional cycles of chemotherapy (6, 23), while other studies have reported that radical surgery is an important component in the multimodal treatment of SCNCC (2, 12, 25).

Although there are few clinical data supporting the use of adjuvant multimodality treatment in early-stage SCNCC, most clinicians favour the use of chemotherapy and/or radiation because of the strong evidence supporting concurrent chemoradiation in other subtypes of cervical cancer and the high incidence of distant metastases in patients with SCNCC (6, 12, 26-28). Patients who received adjuvant radiation, however, had a poorer prognosis than those who did not; even after excluding patients with small tumors (2 cm), adjuvant radiation did not improve outcome. This finding is consistent with another study in wich adjuvant radiation did not alter the course of pelvic recurrence (27). In contrast, chemotherapy has been indicated because adjuvant chemotherapy, though associated with toxicity, resulted in better survival for patients primarily treated with surgery for SCNNC (12, 27, 29).

However, in a very recent retrospective study on 68 patients (18), adjuvant chemotherapy tended to favor survival, but the difference was not statistically significant. When adjuvant chemotherapy and chemo-radiation were compared, the latter did not improve outcomes. Although adjuvant radiation may decrease pelvic recurrence, the lack of improvement in overall survival was likely due to the inability to prevent distant metastasis. In addition, adjuvant radiation plus concurrent chemotherapy may increase toxicity, with subsequent treatment delays. Due to high incidence of early nodal and distant metastasis in early-stage SCNCC, it is likely that adjuvant chemotherapy would enhance survival relative to radiation (18).

Despite the retrospective studies and case reports reported in the literature (Table I), the best modality of treatment remains controversial. Hence, considering the rarity of this ominous disease, multicenter clinical trials are needed to determine a univocal and effective treatment for SCNCC in order to achieve significant survival benefit.

Conflict of Interest

We declare that we have no conflict of interest.

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