Small Cell Carcinoma of the Uterine Cervix: Clinicopathological Analysis of 17 Cases

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From 1981 to 1990, seventeen patients with small cell carcinoma (SCC) of the uterine cervix were studied. Histopathologically, two of them were oat cell type, ten of them were intermediate type, and five of them were combined type with three of them combined with squamous cell carcinoma, one of them combined with adenosquamous carcinoma, and one of them combined with adenocarcinoma. The lympho-vascular invasion was noted in 6 cases. Their survivals were generally poor with a mean survival of 11.4 months. The positive immunohistochemical stainings were noted in 13 cases for synaptophysin, 12 cases for neuron-specific enolase (NSE), 9 cases for neurofilament and cytokeratin, 6 cases for chromogranin. The immunohistochemical stainings for bombesin and adreno-corticotropic hormone were all negative. The clinical and pathological characteristics were described and discussed in the context.

Key Words: small cell carcinoma, uterine cervix, immunohistochemistry.

Introduction

Most small cell carcinomas (SCCs) were reported to occur in the lung. this highly malignant tumor has its distinct clinical and pathological characteristics (1-3) . Recently, more and more extrapulmonary SCCs were reported to occur in the prostate (4,5), urinary bladder (6,7), gall bladder (8), esophagus (9,10), colon (11,12) , breast (13), skin (14) and uterine cervix (15,16). The authors aim more effort in this specific tumor in the hope of resolving the ambiguities concerning the histogenesis and histochemical behavior.

SCC of the uterine cervix is a rare gynecological malignancy, accounting for

less than 5% of cervical cancer (17). The histogenesis of SCC of the uterine cervix is still not entirely clear. The most acceptable hypotheis is that they may arise from argyrophilic cells or their presumed precursors that present in the normal columnar and/or squamous epithelium of the uterine cervix (18).

The purpose of this paper to report seventeen cases of SCC of the uterine cervix, and to represent their clinical and pathological characteristics.

Materials and Methods

Seventeen cases of SCC of the uterine cervix identified by the department of pathology of Tri-Service General Hospital from 1981 to 1990 were obtained. The clinical information including the age, symptom and sign, clinical stage, treatment, and survival were obtained from medical records.

For histopathological study, the formalin-fixed and paraffin-embedded tissue blocks were sectioned at intervals of 5 um, then were stained by hematoxylin and eosin (H&E). The histologic criteria used for the diagnosis of SCC of the uterine cervix were fully described by Silva et al. (19). To be included in this study, all the tissue slides were reviewed and examined carefully.

For immunohistochemical studies, peroxidase-antiperoxidase (PAP) method was performed for seven tumor markers: chromogranin (Enzo), cytokeratin (Enzo), neurofilament (NF) (Immunotech), NSE (Dako), synaptophysin (Boehringer), bombesin (Biomeda), and adrenocorticotropic hormone (ACTH) (Dako). For confirming the specificity of the immunoreaction, the negative and positive control tissue sections were used.

Results

The patients' age ranged from 42 to 62 years with an average of 50.3 years. Abnormal vaginal bleeding was the most common initial symptom, only three patients suffered from dysmenorrhea as the initial symptom. The therapeutic methods were variable, radical hysterectomy with bilateral pelvic lymphadenectomy followed by chemotherapy or radiotherapy or both. The survival time ranged from 5 months to 26 months, with a mean survival of 11.4 months. All the clinical details were summerized in table I.

According to the histologic criteria for SCC of uterine cervix as defined by Silva and coworkers (19), the tumors mainly composed of sheets of small, round, oval (Fig. 1), polygonal, or fusiform (Fig. 2) tumor cells with scant cytoplasm. Three cases showed combined with squamous cell carcinoma (Fig. 3), one case showed combined with adenosquamous carinoma, and one case show combined with adenocarcinoma (Fig 4). Lympho-vascular invasion was noted in 6 cases. The perivascular basophilic deposition can be found only in 1 case. All the histopathological findings were summarized in table II. The results of the immunohistochemical staining for the seven tumor markers were shown in table III. The synaptophysin immunoreaction showed positive in 13 cases (Fig. 5), whereas the NSE in 12 cases (Fig. 6), NF and cytokeratin in 9 cases (Fig. 7, Fig. 8) and chromogranin in 6 cases (Fig 9). No immunoreaction was found for
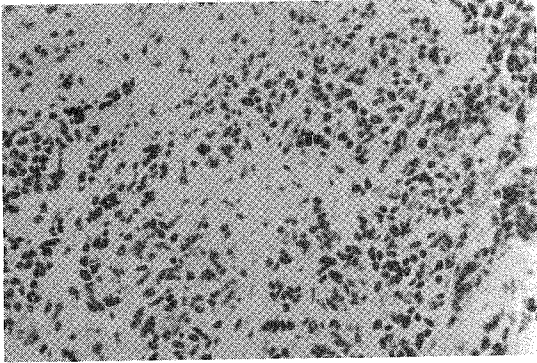
Fig. 1. Oat cell type small cell carcinoma of the uterine cervix. The tumor cells show small, round or oval with scant cytoplasm. (H & E, X200)
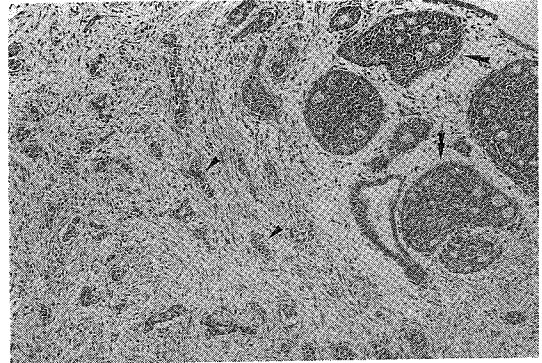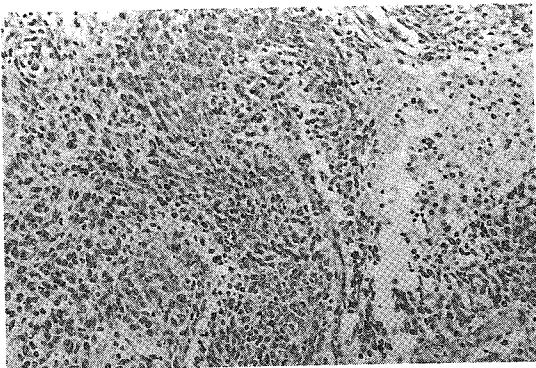

Fig. 2. Intermediate type small cell carcinoma of the uterine cervix. The tumor cells show spindle or polygonal shape with scant cytoplasm. (H & E, X200)

Fig. 3. Small cell carcinoma (arrow) combined with squamous cell carcinoma (double arrow). (H & E, X200)

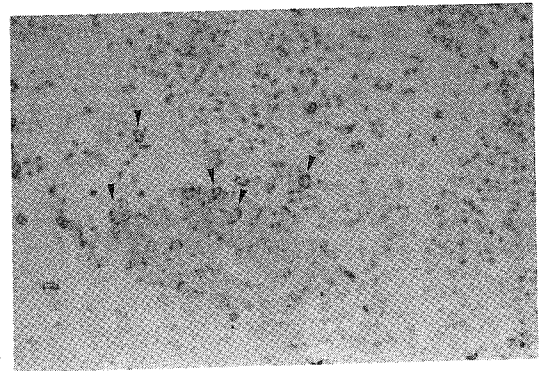Fig. 4. Small cell carcinoma (arrow) combined with adenocarcinoma (double arrow). (H & E, X100)

Fig. 5. Small cell carcinoma of the uterine cervix with positive immunostaining for synaptophysin (arrow). (PAP, X200)

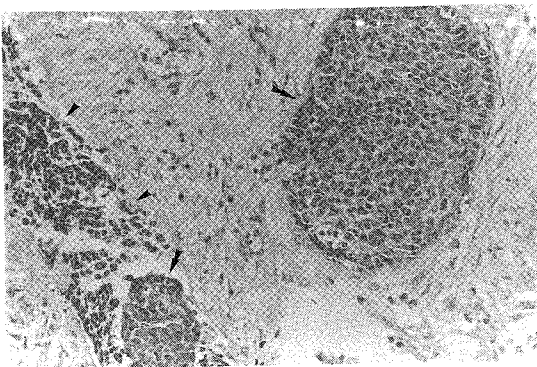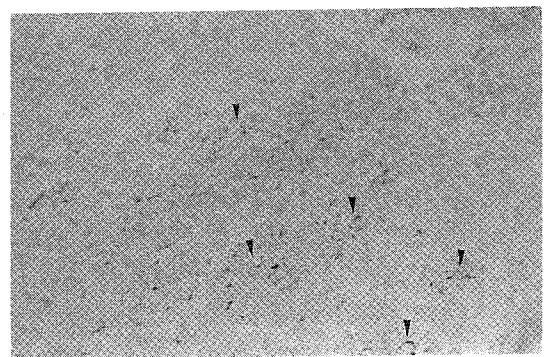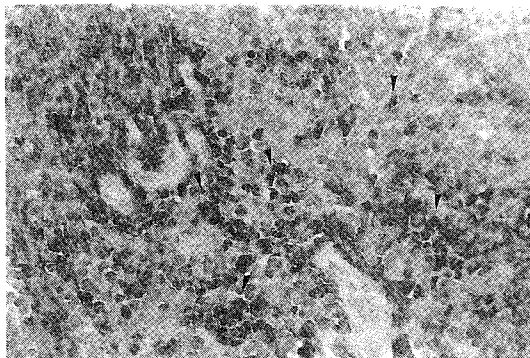Fig. 6. Small cell carcinoma of the uterine cervix with positive immunostaining for NSE (arrow). (PAP, X200)

Fig. 7. Small cell carinoma of the uterine cervix with positive immunostaining for neurofilament (arrow). (PAP, X200)
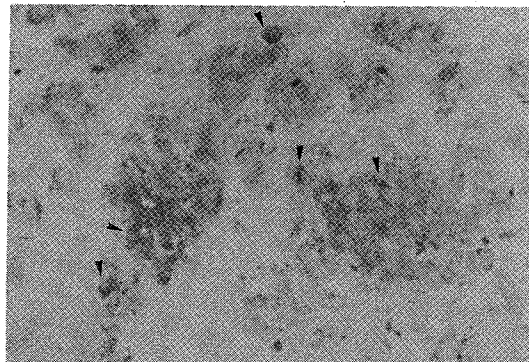

Fig. 9. Small cell carcinoma of the uterine cervix with positive immunostaining for chromogranin (arrow). (PAP, X400)
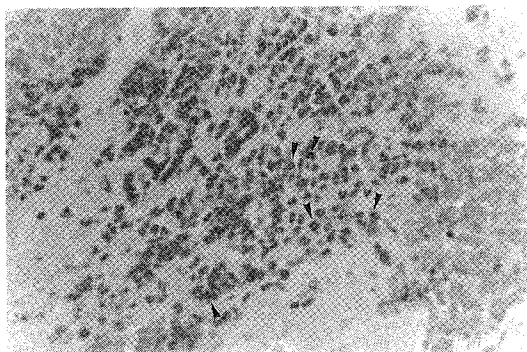
Fig. 8. Small cell carcinoma of the uterine cervix with positive immunostaining for cytokeratin (arrow). (PAP, X200)

Table 1. Clinical Details of 17 SCCs of the Uterine Cervix

Case	Age	Initial S/S*	clinical stage	Treatment	Survival
1	48	vaginal bleeding	IIa	S+R+C**	9 months
2	46	vaginal bleeding	Ib	S+R+C	14 months
3	52	vaginal bleeding	Ib	S+R	8 months
4	43	dysmenorrhea	Ib	S+R	16 months
5	53	vaginal bleeding	Ib	S+R+C	26 months
6	42	dysmenorrhea	IIb	S+R	5 months
7	49	vaginal bleeding	IIb	S+C	7 months
8	44	vaginal bleeding	IIb	R	6 months
9	57	vaginal bleeding	Ib	S+R+C	12 months
10	53	vaginal bleeding	Ib	S+R	8 months
11	59	vaginal bleeding	Ib	S+R	18 months
12	56	vaginal bleeding	IIa	S+R+C	11 months
13	62	vaginal bleeding	Ib	S+R+C	9 months
14	47	dysmenorrhea	Ib	S+R+C	13 months
15	44	vaginal bleeding	IIa	S+R	11 months
16	53	vaginal bleeding	Ib	S+R	16 months
17	47	vaginal bleeding	IIb	R	5 months

* S/S=symptom and sign
** S =surgery, R=radiotherapy, C=chemotherapy

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Table 2. Main Histopathologic Features of 17 SCCs of the Uterine Cervix

Case	Histologic type	Perivascular basophilic deposition	Lympho-vascular invasion
1	combined	−	+
2	intermediate	−	−
3	oat cell	−	−
4	combined	−	−
5	intermediate	−	−
6	intermediate	−	+
7	oat cell	−	+
8	combined	−	+
9	intermediate	−	−
10	intermediate	−	−
11	combined	−	−
12	intermediate	−	+
13	intermediate	−	−
14	intermediate	+	−
15	intermediate	−	+
16	intermediate	−	−
17	combined	−	−

Table 3. Immunohistochemical Findings of 17 SCCs of the Uterine Cervix

Case	NSE	NF	CK	CHR	SYN	BOM	ACTH
1	+	+	+	−	+	−	−
2	+	+	+	+	+	−	−
3	+	+	+	−	+	−	−
4	−	+	+	+	−	−	−
5	+	−	−	−	+	−	−
6	−	+	−	−	−	−	−
7	+	−	−	−	+	−	−
8	+	+	−	+	−	−	−
9	−	−	+	+	+	−	−
10	+	−	+	−	−	−	−
11	+	−	+	−	+	−	−
12	−	−	+	+	+	−	−
13	+	−	−	−	+	−	−
14	+	+	−	+	+	−	−
15	−	+	−	−	+	−	−
16	+	−	−	−	+	−	−
17	+	+	+	−	+	−	−

NSE = neuron − specific enolase
NF = neurofilament
CK = cytokeratin
CHR = chromogranin
SYN = synaptophysin
BOM = bombesin
ACTH = adrenocorticotropic hormone
+ = positive
− = negative

bombesin and ACTH.

Discussion

The age distribution of SCC of the uterine cervix ranged from 21 to 78 years (20). In general, the tumor occurred most common after the years of 50 (2,21). In this study, the patients' age ranged from 42 to 62 years, which were consistent with those of previous reports. As same as the previous reports (16,22,23), the most common initial symptom for SCC of the uterine cervix was abnormal vaginal bleeding. Although it has been reported that SCC of the uterine cervix may produce some hormone such as ACTH, insulin, and vasoactive amine (15,23,24), however patients with SCC of the uterine cervix with paraneoplastic syndrome is very rare. In this study no patient with paraneoplastic syndrome was found. According to our study and previous reports (16,22,25,26), we suggest that radical hysterectomy was not adequate for the treatment of SCC of the uterine cervix, combined chemotherapy and radiotherapy must be included. However, the survival of SCC of the uterine cervix was generally poor and worse than that of other types of cervical carcinoma. Huang et al (22) reported that the 2-year survival rate of SCC of the uterine cervix was 14%. The clinical stage has great influence on the survival of SCC of the uterine cervix. Nagell et al (25) reported that SCC of the uterine cervix in stage III and stage IV had 100% recurrent rate. Yamasaki et al (26) reported that the 5-year survival rate for SCC of the uterine cervix was 40% in stage I and 0% for patients in stage II and III. According to the previous report (25) the 5-year sur-

vival rate for SCC of the uterine cervix was 55% ± 10% versus 68% ± 9% for large cell non-keratinizing squamous cell carcinoma and 74% ± 9% for large cell keratinizing squamous cell carcinoma.

The histologic criteria for extrapulmonary SCC are as same as the pulmonary SCC, which was proposed by WHO in 1981 (27). The SCC is divided into three subtypes: oat cell type, intermediate type, and combined type. In this study, 2 cases were oat cell type, 10 cases were intermediate type, and 5 cases were combined type. In the combined type, 3 cases combined with squamous cell cacinoma, 1 cases combined with adenosquamous carcinoma, and 1 case combined with adenocarcinoma. The tumor cells often group as sheet or arranged as trabecula. The tumor cells of oat cell type show uniform, small, round or oval with dense nuclei and scant cytoplasm. In contrast to the oat cell type, the tumor cells of the intermediate type show spindle or polygonal with more abundant cytoplasm. A very characteristic histopathologic picture of the pulmonary SCC is the perivascular basophilic deposition, which is known as Azzopardi's phenomenon and said to be the result of deposition of nucleic acid (28), however it is uncommon in the SCC of uterine cervix. In this study only one case had such phenomenon. The lympho-vascular invasion can often be found in SCC. It has been reported that about 60% of SCC of the uterine cervix had lympho-vascular invasion at the time of diagnosis (26,29,30). In this study, 6 cases had significant lympho-vascular invasion.

According to previous reports (31-34), NSE is a useful tumor marker for pul-

monary SCC. In SCC of the uterine cervix, NSE immunostaining also show positive frequently (35). Huang et al (22) reported that 8 of 9 cases of SCC of the uterine cervix were positively stained by NSE. As same as plumonary SCC, the positive NSE immunostaining in SCC of the uterine cervix indicates that such tumors are of neuronal origin. NF is said to be distributed in tumors of neural or neuroendocrine origin (36-39). In SCC of uterine cervix, the positive immunostaining for NF can also be found, but it is less frequent than that for NSE. In contrast to NF, a high positive immunoreaction (76.5%) for synaptophysin could be demonstrated in SCC of the uterine cervix. It is our suggestion, that synaptophysin may act as a useful tumor marker for SCC for the uterine cervix. It has been reported that chromogranin is an universal tumor marker for neuroendocrine cells and tumors (40-43). Van Nagell et al's report showed that chromogranin immunoreaction could be demonstrated in SCC arising from the uterine cervix (25). In this study only 6 cases revealed positive immunoreaction for chromogranin. For the low positive rate (35.3%), chromogranin is not suggested as a useful tumor marker for SCC of the uterine cervix. For tumors of epithelial origin, cytokeratin is considered as a trustable tumor marker. In the neuroendocrine tumor such as pulmonary SCC, the immuno-reaction for cytokeratin could also be demonstrated (21). It has been reported that cytokeratin immunoreaction could also be demonstrated in SCC of the uterine cervix (22,25). In this study, 9 cases (52.9%) revealed such immunoreaction. It is our experience that the various positive rate may be due to the different cytokeratin with various molecular weight. According to the previous studies (21,44) bombesin is also suggested to be a tumor marker for neuroendocrine tumors including the SCC especially for pulmonary SCC. However, no such immmunoreaction was found in this study. It is our opinion that bombesin is a useful tumor marker for pulomoary SCC but not for SCC of the uterine cervix. Although SCC of the uterine cervix with ectopic ACTH production has occasionally been reported (15,23,45), the positive ACTH immunostaining in SCC of the uterine cervix is generally rare. Huang et al (22) reported that all SCCs of the uterine cervix were negatively stained by ACTH. In this study, all the cases revealed negative immunostaining for ACTH, which is compatible with most of the previous reports. In conclusion, we emphasize that SCC of the uterine cervix is a highly malignant tumor with poor prognosis. Not only the distinct histopathological characteristics, but also the immunohistochemical properties is useful tools for the accurate diagnosis of SCC of the uterine cervix.

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子宮頸小細胞癌：
17病例之臨床與組織病理分析

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　　小細胞癌最早是在肺部發現，而後陸續有報告發生在其他器官如：攝護腺、膀胱、胃腸道、皮膚和子宮頸等，本文共收集17例子宮頸小細胞癌，針對其臨床和組織病理變化加以分析。病人的年齡分佈在42歲到62歲，而平均為50.3歲，不正常陰道出血乃最常見之症狀，平均存活期為11.4月，17例中有12例為純小細胞癌而有5例為混合型，包括3例混合鱗狀上皮癌，1例混合鱗狀上皮癌和腺癌，而1例混合腺癌，免疫組織化學染色synaptophysin有13例為陽性，neuronspecific enolase有12例為陽性，neurofilament和cytokeratin各有9例為陽性，chromogranin有6例為陽性，bombesin在所有病例則均為陰性反應，由以上免疫組織化學染色和組織學上常合併出現其他型態上皮性腫瘤分化之特性，顯示子宮頸小細胞癌同時具有上皮細胞和神經細胞來源之雙重特性。

關鍵字：小細胞癌、子宮頸、免疫組織化學

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