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Differential expression of neuroendocrine markers, TTF-1, p53, and Ki-67 in cervical and pulmonary small cell carcinoma

Haiping Liu, MD, Yan Zhang, MM, Jianfang Chang, MM, Zhitao Liu, MM, Ning Tang, PhD*

Abstract

Small cell carcinoma (SCC) is a highly malignant neuroendocrine tumor that may occur in many anatomic sites of the body.

In this study, we compared the different expression of neuroendocrine markers, thyroid transcription factor 1 (TTF-1), p53, and Ki-67 in 23 cases of cervical SCC and 56 cases of pulmonary SCC using immunohistochemistry.

Our study showed that cervical SCC had a younger onset age than pulmonary counterpart. Although both had the similar morphological features, different immunohistochemical expression panel was observed in this study. As neuroendocrine tumors, SCC of cervix and lung had similar immunoreactive staining for CD56 and chromogranin A, but the expression of the synaptophysin in cervical SCC was significantly higher than that in pulmonary SCC ($P = .007$). The TTF-1 expression of pulmonary SCC illustrating diffuse and strong positivity in tumor cell nuclei was significantly higher than that of the cervical SCC ($P = .003$). There was only 1 case showing p53 protein over-expression in the 23 cases of cervical SCC, and p53 over-expression was observed in 42.9% of pulmonary SCC ($P = .001$). Only 9 cases of cervical SCC showed ≥80% of the Ki-67 proliferation index, while it was found in 94.6% of pulmonary SCC ($P < .001$).

The different immunohistochemical expressions of these 2 kinds of SCCs may be related with their pathogenetic mechanism, and these differences may be helpful in the identification of the origins of the metastatic SCC with unknown primary site.

Abbreviations: CgA = chromogranin A, HPV = human papillomavirus, SCC = small cell carcinoma, Syn = synaptophysin, TTF-1 = thyroid transcription factor 1.

Keywords: cervix, chromogranin A, lung, p53, small cell carcinoma, thyroid transcription factor 1

1. Introduction

Small cell carcinoma (SCC) is a kind of highly malignant neuroendocrine tumor that may occur in every part of the body, most commonly in lungs, which takes 95% of all the SCC cases.[1] SCC may also be found in digestive tract, cervix, ovary, bladder, prostate, and endometrium.[2–5] Although SCC can be found in different anatomic sites, similarities, such as histological appearance, immunohistochemical expression of epithelial and neuroendocrine markers, common involvement of lymph nodes and vessels invasion, hematogenous metastasis, and unfavorable prognosis, can be observed.[3] However, the risk factors are usually different. Pulmonary SCC mostly attacks heavy smokers.[1] Although smoking is also a risk factor for cervical cancer, it is not a confirmed factor for cervical SCC. The relationship between high-risk human papillomavirus (HPV) and cervical SCC has already been confirmed by many studies.[6,7] However, HPV-associated SCC was rarely reported in other anatomic sites except in cervix and oropharynx.[8] The diagnosis of SCC mainly depends on immunohistochemistry to distinguish from squamous cell carcinoma, adenocarcinoma, and lymphoma. The previous researches mostly focused on SCC in a single body part, thereby lacking comparison in different anatomic sites, though Maria et al have systematically summarized the reported cases of genital tract SCC, including SCCs in cervix, endometrium, ovary, fallopian tube, and vagina in the English literature from 1972 to 2014.[9] This research adopted immunohistochemical methods to find the expression differences of neuroendocrine markers, as well as thyroid transcription factor 1 (TTF-1), p53, and Ki-67 in SCC of cervix and lung. The differential expression may be helpful in identifying the origin of metastatic SCC with unknown primary site.

2. Materials and methods

2.1. Clinical materials

The pathologically diagnosed cervical and pulmonary SCC cases were collected in our hospital from January 2012 to May 2017. There were 23 cervical SCC cases, including 5 biopsy specimens and 18 surgical excision specimens. And there were 56 cases of pulmonary SCC, including 40 cases of bronchoscopy biopsy specimens or percutaneous lung puncture biopsy specimens, and

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The study was approved by the Ethical Committee of the General Hospital of Jinan Military Command. Written informed consent was obtained from the patients involved in the study.

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Reproductive Medicine Center, General Hospital of Jinan Military Command, Jinan, Shandong, China.

* Correspondence: Ning Tang, Reproductive Medicine Center, General Hospital of Jinan Military Command, Jinan, Shandong 250031, China (e-mail: ningtang423@163.com).

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16 cases of surgical excision specimens. The pulmonary SCC patients included 43 males and 13 females. The research was approved by the Ethics Committee of the General Hospital of Jinan Military Command, and the written informed consents were signed by the patients.

2.2. Methods

All the specimens were fixed in 10% neutral formalin with treatments of conventional dehydration, waxdip, embedding, slicing into 4 μm thick slices and hematoxylin–eosin staining. Then the histomorphology was observed under the light microscope. The Roche Ventana BenchMark XT systematic immunohistochemical apparatus (Ventana Medical Systems, Inc, Tucson, AZ) was used to perform immumohistochemical staining. The primary antibodies included CD56 (neural cell adhesion molecule, Maixin Biotech Co. Ltd [MXB], clone: 56C04), chromogranin A (CgA, MXB, clone: LK2H10 + PHE5), synaptophysin (Syn, MXB, clone: SP11), TTF-1 (MXB, clone: SPT24), p53 (DAKO, clone: DO-7), and Ki-67 (DAKO, clone: MIB-1). The second antibody Ultraview Universal DAB Detection Kit was purchased from Roche Diagnostics Ltd. The positive and negative contrasts were carried out in every experiment.

2.3. Determination of results

CD56 positive staining located in the cytomembrane, the positive location of CgA and Syn was in the cytoplasm, and the positive location of TTF-1 and Ki-67 was in the cell nucleus. Except p53 and Ki-67, the positive was defined as that ≥10% of tumor cells were stained with brownish yellow at medium or above level; the positive of p53 was defined as that ≥50% tumor cell nuclei showed strongly positive; and percentage count was used for Ki-67 proliferation index. Cell count was performed using the software of Image-Pro Plus 6.0.

2.4. Statistical methods

Statistical software SPSS17.0 (SPSS, Inc, Chicago, IL) was adopted in this research. Pearson chi-squared test or Fisher exact test was employed for correlation analysis of enumeration data, and rank-sum test was used for measurement data. $P < .05$ was considered as the difference of statistical significance.

3. Results

3.1. Clinical materials

This research included 79 SCC patients enrolled in this study including 23 cases of cervical SCC and 56 cases of pulmonary SCC. The onset age of cervical SCC was from 31 to 74 years, and the mean age was 41 years. Cervix exophytic mass or erosion and anabrosis were observed by gynecologic examination. The clinical manifestations and signs of most patients were not significantly different comparing with common cervical cancer cases, because of the main symptoms of cervical contactive bleeding or irregular vaginal bleeding. Only 1 case with 40-year old showed the symptoms of paraneoplastic syndrome—unsteadiness of walking and dizziness and nausea. Twelve cases of cervical SCC were single tumor, and the other 11 cases manifested as compound SCC, including 6 cases with squamous cell carcinoma, 2 cases with adenocarcinoma, and 3 cases with squamous cell carcinoma in situ. One patient with cervical SCC received preoperative radiotherapy and chemotherapy. There were 56 pulmonary SCC patients with the onset age from 35 to 78 years old and a mean age of 58 years old. The main symptoms of these patients were chest distress, chest ache, cough, and hemoptysis. Twenty-four patients with pulmonary SCC received preoperative radiotherapy and chemotherapy. The onset age of cervical SCC was younger than that of the pulmonary SCC (rank-sum test, $P < .05$).

3.2. Pathological and morphological characteristics

Cervical and pulmonary SCC tumor cells had similar morphological characteristics (Figs. 1A and 2A). The tumor was composed of a uniform population of closely packed small cells with an extremely high nuclear-to-cytoplasmic ratio. The nuclei were oval and densely hyperchromatic with indistinct nucleoli. Tumor cells were diffusely infiltrating in solid sheets or cord-like structures. Mitotic figures and necrosis were commonly found. Artificial extrusion was commonly seen in biopsy specimens.

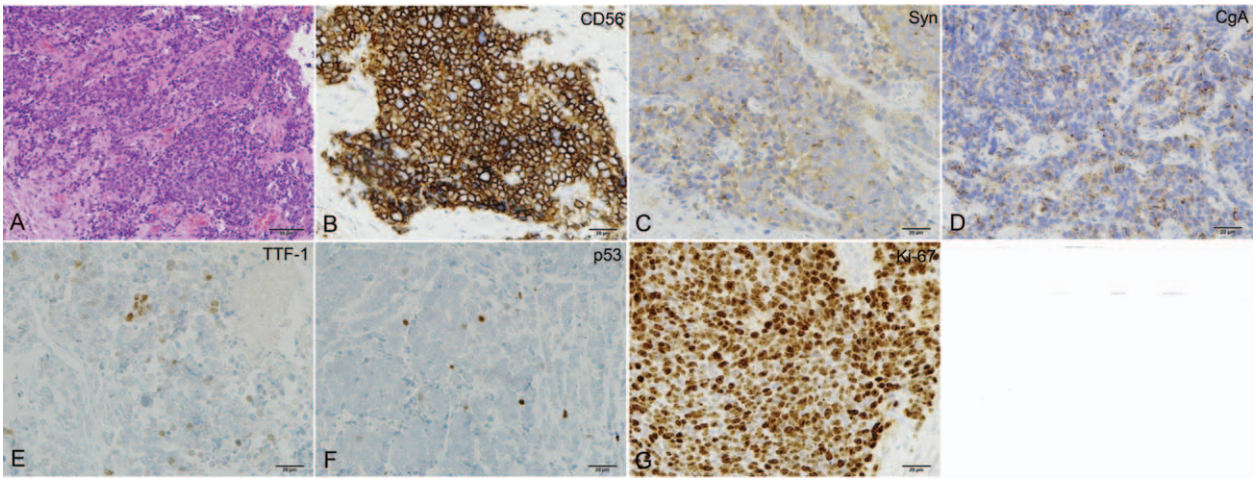

Figure 1. The immunohistochemical features of cervical SCC. (A) The tumor was composed of small round cells arranged in the nest-like structure (HE, ×200); the tumor cell showed positive for CD56 (B), Syn (C), and CgA (D). (E) About 25% of tumor cells showed weakly positive for TTF-1; (F) about 5% of tumor cells was positive for p53; (G) Ki-67 staining showed positive for about 75% of tumor cells (B–G: immunohistochemistry, ×400). CgA = chromogranin A, HE = hematoxylin and eosin, SCC = small cell carcinoma, Syn = synaptophysin, TTF-1 = thyroid transcription factor 1.

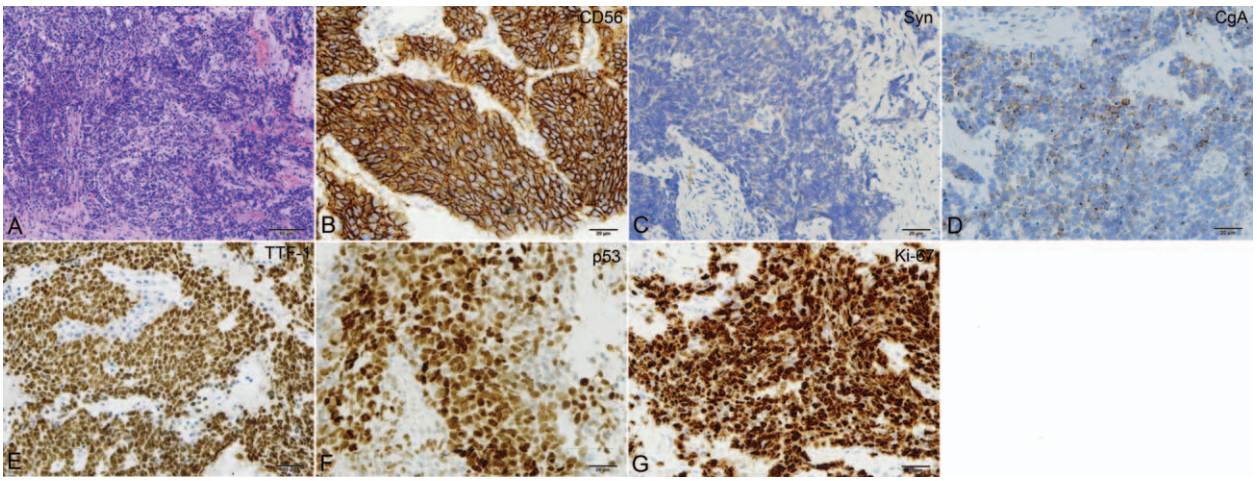

Figure 2. The immunohistochemical features of pulmonary SCC. (A) The tumor was composed of small round cells arranged in the nest-like structure (HE, ×200); (B) the tumor cell showed positive for CD56; (C) Syn was negative in cervical SCC; (D) the tumor cell showed positive for CgA; (E) almost all tumor cells showed strongly positive for TTF-1; (F) about 80% of tumor cells expressed p53 protein; (G) Ki-67 staining showed positive for about 90% of tumor cells (B–G: immunohistochemistry, ×400). CgA = chromogranin A, HE = hematoxylin and eosin, SCC = small cell carcinoma, Syn = synaptophysin, TTF-1 = thyroid transcription factor 1.

3.3. Immunohistochemical results

The tumor cells of SCC showed various expressions of neuroendocrine markers (Tables 1 and 2, Figs. 1B–D and 2B–D). There were 91.1% (72/79) of the CD56 expressions of SCC in this research with the positive rates of 91.3% and 91.1% for cervical and pulmonary SCC, respectively, which are similar in both groups (Table 2, $P=1.00$). The total positive rate of Syn in SCC was 69.6% (55/79), with the positive rates of 91.3% and 60.7% for cervical SCC and pulmonary SCC, respectively, showing higher Syn expression of cervical SCC (Table 2, $P=.007$). The positive rate of CgA in SCC was 68.4% (54/79), and they were 82.6% and 62.5% for cervical and pulmonary SCC, respectively. There was no significant difference for the CgA protein expression between the 2 groups in statistical analysis ($P=.081$). The positive rates of TTF-1 in cervical and pulmonary SCCs were 73.9% and 96.4%, respectively. A statistically significant difference between the 2 groups was observed ($P=.003$). The percentage of TTF-1 positive cells in cervical SCC ranged from complete negative to 95%, and the staining score was also from faint yellow to dark brownish yellow (Fig. 1E). Six cases of cervical SCC showed negative expression of TTF-1, and 9 cases showed strong positive of ≥50% of the tumor cells (Table 1). Most of the pulmonary SCC showed strong positive of ≥70% of the tumor cell nuclei (Fig. 2E). However, 2 patients manifested weak positive expression of <10% of the tumor cells. The immunohistochemical p53 expression in most cervical SCCs showed tumor cells were positive ranging from negative to 35% (Fig. 1F). The positive intensity was light to medium brownish-yellow. There were 16 cases of cervical SCC with p53 positive cells <10%, and only 1 case showed positive expression for p53 protein. This case was synchronously accompanied by squamous cell carcinoma, which was also immunohistochemical positive for p53 protein (Fig. 3). In the 56 cases of pulmonary SCC, there were 24 cases of over-expression of p53 with ≥50% of tumor cells showing diffuse dark brownish yellow (Fig. 2F). The immunohistochemical p53 protein expression in both cervical and pulmonary SCCs had significant differences ($P=.001$); 94.6% of the pulmonary SCCs showed that ≥80% of the tumor cells were Ki-67 positive (Fig. 2G). Cervical SCCs showed that 25% to 85% of the tumor cells were Ki-67 positive, and the proportion of positive tumor cells in most cases was ranged from 50% to 80% (Fig. 1G). There were 2 cases of cervical SCC with tumor cell Ki-67 proliferation index <50%. The comparison of Ki-67 proliferation indexes in cervical and pulmonary SCCs showed that there was significant difference between the 2 groups by rank-sum test. The comparison of the

Table 1

Detailed distribution of staining scores (in % positive) of all biomarkers in cervical and pulmonary small cell carcinomas.

	Cervical small cell carcinoma				Pulmonary small cell carcinoma			
Antibodies	**<10%, n**	**10–25%, n**	**25–50%, n**	**≥50%, n**	**<10%, n**	**10–25%, n**	**25–50%, n**	**≥50%, n**
CD56	2	3	4	14	5	7	8	36
Syn	2	3	7	11	22	15	10	9
CgA	4	5	6	8	21	17	10	8
TTF-1	6	4	4	9	2	3	4	47
p53	16	5	1	1	8	10	14	24
Ki-67	0	0	2	21	0	0	2	54

CgA = chromogranin A, Syn = synaptophysin, TTF-1 = thyroid transcription factor 1.

Table 2

Immunohistochemical expression of neuroendocrine markers, TTF-1, p53, and Ki-67 in cervical and pulmonary small cell carcinomas.

Antibodies	Cervical SCC		Pulmonary SCC		χ^2	*P*
	Positive, n	Negative, n	Positive, n	Negative, n		
CD56	21	2	51	5	0.001	1.000
Syn	21	2	34	22	7.213	.007
CgA	19	4	35	21	3.048	.081
TTF-1	17	6	54	2	9.082	.003
p53	1	22	24	32	11.177	.001
Ki-67*	9	14	53	3	29.750	<.001

CgA = chromogranin A, SCC = small cell carcinoma, Syn = synaptophysin, TTF-1 = thyroid transcription factor 1.
* Ki-67 positivity refers to that ≥80% of the tumor cell nuclei were strongly stained.

Ki-67 proliferation indexes of the 2 groups also showed significant difference between the 2 groups by Pearson chi-squared test ($P < .001$), with 80% as the cut-off value.

4. Discussion

SCC is a highly malignant neuroendocrine tumor that may occur in many anatomic sites of the body. Pulmonary SCC accounts for 10% to 20% of all the pulmonary cancer cases,[10] and occurs mainly in middle-aged and elderly males. More than 80% of the cases involve males with the mean onset age of 60 years old. They sometimes show superior vena cava syndrome because of rapid growth and early metastasis of pulmonary SCC. In this study, a total of 56 cases of pulmonary SCC patients, including 43 male cases and 13 female cases, showed onset age of 35 to 78 years old, and the mean onset age was 58 years old. The clinical symptoms were mainly cough and hemoptysis. Cervical SCC cases are relatively rare, and account for 0.9% of all the cervical infiltrating malignancies.[11] Zhou et al analyzed the Surveillance, Epidemiology, and End Results database, and reported 487 cases of cervical SCC[3]; the onset age ranged from 19 to 95 years old, and the mean onset age was 49 years. The onset age of the 23 cases of cervical SCC in this research was 31 to 74 years old and the mean onset age was 41 years, which was close to the mean onset age

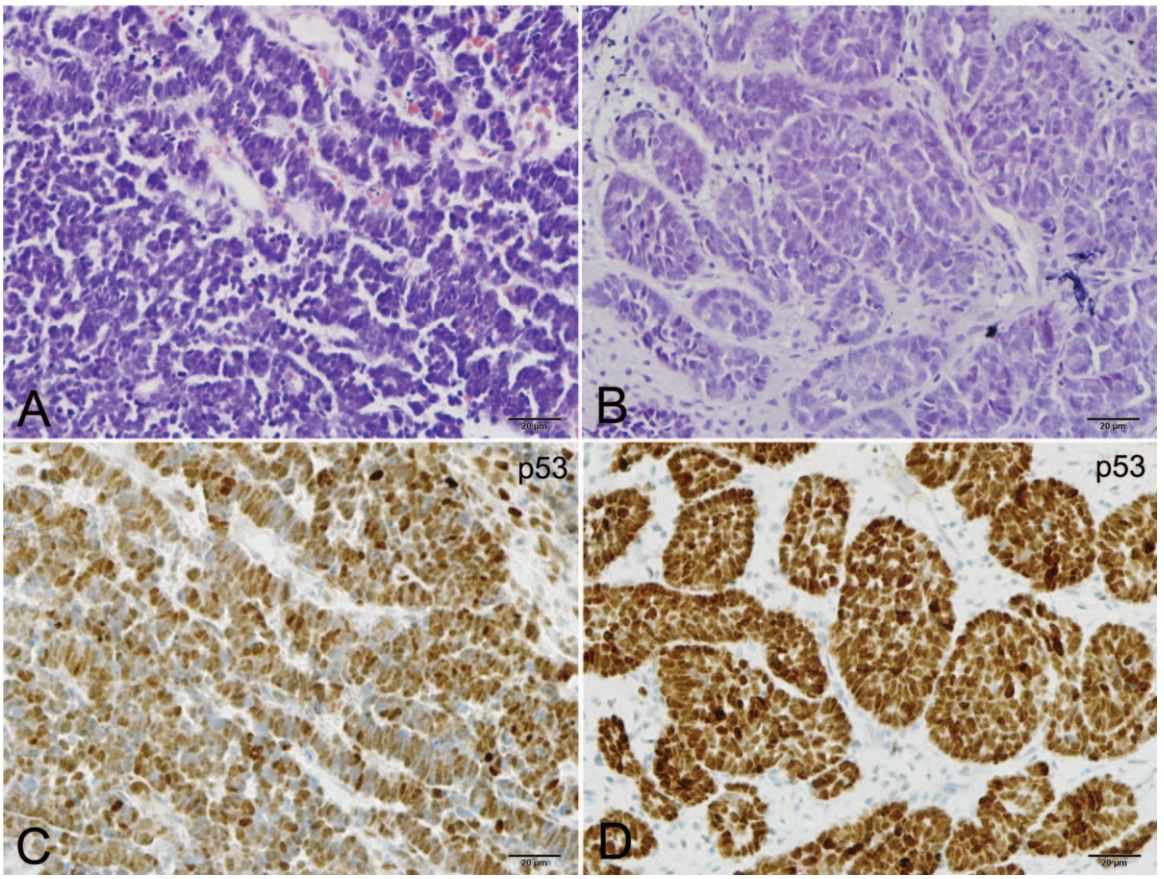

Figure 3. A case of cervical SCC was synchronously accompanied by squamous cell carcinoma. (A) Cervical SCC (HE, ×400); (B) squamous cell carcinoma (HE, ×400); (C) tumor cells of SCC were positive for p53 protein (immunohistochemistry, ×400); (D) tumor cells of squamous cell carcinoma were positive for p53 protein (immunohistochemistry, ×400). HE = hematoxylin and eosin, SCC = small cell carcinoma.

reported in the literature. The symptoms of the patients were mainly contact bleeding or irregular vaginal bleeding. In this study, 1 patient represented paraneoplastic syndrome which often occurs in patients with pulmonary SCC.[12]

The histogenesis of SCC has always been in dispute. At present, SCC is believed to have originated from pluripotent stem cells or precursor multipotent cells with neuroendocrine differentiations in mucosa epithelium but differentiated neuroendocrine cells. Although pulmonary and cervical SCCs have similar morphological features and biological behavior, their mechanisms may be different. The occurrence of cervical SCC is closely related to HPV, especially high-risk HPV (HPV 18/16), which is similar to cervical squamous cell carcinoma and adenocarcinoma. Horn et al have confirmed that high-risk HPV infection and the development of cervical SCC were significantly correlated, and HPV18 protein inactivation was the main factor in the incidence of cervical SCC.[13] Herrington has also confirmed the relationship between cervical SCC and high-risk HPV infection by in situ hybridization.[14] However, HPV infection generally cannot be detected in SCC of lung, digestive tract, ovary, bladder, prostate, and other parts of the body.

SCCs mainly showed different expressions of neuroendocrine markers. It was generally believed that CD56 antibody was highly sensitive, and CgA and Syn had strong specificity.[15] These 3 antibodies were often used together in the pathological diagnosis to distinguish SCC from squamous cell carcinoma, adenocarcinoma, lymphoma, and other malignant tumors. CD56 antibody was a protein marker with the most stable expression in SCC with the highest positive rate. Tumor cells usually revealed diffuse membrane expression. CD56 expression had the highest positive rate among the 3 neuroendocrine markers adopted in this research. Although Syn and CgA were commonly used immnunohistochemical markers for diagnosis of SCC, different positive rates of each antibody were reported either in cervical SCC or in pulmonary SCC in different studies.[16,17] It was found that Syn had higher expression in the cervical SCC than in the pulmonary SCC in this research, which might be caused by the deviation of specimen selection.

TTF-1 was an immunohistochemical marker widely used in pulmonary and thyroid tumors. Pulmonary primary adenocarcinoma and SCC mostly expressed TTF-1 protein, but it was also reported that TTF-1 was also positive in the extrapulmonary primary SCC.[18] In this research, the TTF-1 positive rate of cervical SCC was 73.9%, but the positive proportion of tumor cells was mostly $<50\%$, and the staining intensity was mostly moderate or weakly. Moreover, some of the tumor tissue showed completely negative expression. This result was completely different from the expression pattern of TTF-1 in pulmonary SCC, which was mostly expressed as diffuse dark brownish yellow staining. Therefore, although TTF-1 was not used as a specific marker of pulmonary primary tumors in the detection of SCC, its positive expression pattern was helpful in distinguishing its origin from cervix or lung.

The P53 gene is an antioncogene as a cell cycle regulator. When the DNA is damaged, the expression products would increase in sharply, which could inhibit the process of the cell cycle. P53 gene mutation or over expression is considered as an indicator of poor prognosis in some malignancies.[19] In this study, the expressions of p53 protein in cervical and pulmonary SCCs were significantly different, which might be related to their mechanism. Cervical SCC was generally associated with high-risk HPV infection, especially HPV 18 and HPV 16. The viral oncoprotein HPV E6 could interact with p53 protein to degrade the latter, making the lower expression of p53 protein,[20,21] which was consistent with the result that 22 cases of cervical SCC did not over-express p53 in this study. It had been reported that 57.1% of pulmonary SCC had mutations in exon 5 to 8 of the p53 gene,[22] which might be related to the over-expression of p53 in pulmonary SCC. Interesting, in this study, p53 protein was over-expressed in 1 case of cervical SCC, and the patient was synchronously accompanied by squamous cell carcinoma with over-expression of p53 protein. We think that the over-expression of p53 protein in cervical SCC might be related with the similar tumor mechanisms of both squamous cell carcinoma and SCC.

Immunohistochemical expression of Ki-67 could reflect the tumor proliferative activity, which was meaningful in the determination of the malignant grade and prognosis of the tumor. Ki-67 in the SCC tissue was highly expressed in this research, with a common proliferation index of $\geq 80\%$; this was a useful indicator to determine the tumor prognosis and to indicate the tumor type; 78.5% of the tumors in the 79 cases of SCC in this study showed Ki-67 proliferation index was $\geq 80\%$. Such results indicated high proliferation activity and invasive potential and high malignancy. The proliferation index of Ki-67 in cervical SCC was mostly between 50% and 80%, and the positive rate was lower than that in the pulmonary SCC, which might be related to the longer survival of cervical SCC than that of pulmonary SCC.

In short, SCC could occur in many anatomic sites of the body. Cervical and pulmonary SCCs had similar morphological characteristics. However, their immunohistochemical expressions were not exact match. Syn in cervical SCC was more likely to be positively expressed, whereas p53 would not be over-expressed. Moreover, the TTF-1 positive rate and positive intensity in cervical SCC were usually lower than that in the pulmonary SCC. The proliferation index of cervical SCC was lower than that of the pulmonary SCC. In our study, differential immnunohistochemical expression in cervical and pulmonary SCCs might be due to the different pathogenesis of both diseases. In addition, immunohistochemistry may be helpful in identifying the origin of the tumor when metastatic SCC was diagnosed with unknown primary site.

Author contributions

Conceptualization: Haiping Liu, Ning Tang.
Data curation: Haiping Liu, Yan Zhang, Jianfang Chang, Zhitao Liu, Ning Tang.
Formal analysis: Haiping Liu, Yan Zhang, Jianfang Chang, Zhitao Liu, Ning Tang.
Investigation: Haiping Liu, Zhitao Liu.
Project administration: Haiping Liu, Ning Tang.
Writing – original draft: Haiping Liu, Yan Zhang, Jianfang Chang, Ning Tang.
Writing – review and editing: Haiping Liu, Ning Tang.

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