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Progress in Diagnosis and Treatment of Small Cell Carcinoma of the Cervix

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ABSTRACT Small cell carcinoma of the cervix (SCCC) belongs to the neuroendocrine carcinomas, and it is a rare gynecological tumor of high-potential malignancy. It has a poorer prognosis compared to cervical squamous cancer or adenocarcinoma, and the therapeutic regimen of the disease differs. Diagnosis is based on pathomorphological characteristics, i.e., the small and round cancer cells (oat cell) which are uniform in shape and size, with the immunohistochemical marker helpful for diagnosis. Combined therapy is first recommended. Postoperative chemotherapy with platinum/etoposide (PE), vincristine/adriamycin/cyclophosphamide (VAC) and taxel/carboplatin (TP) can markedly improve the prognosis of early SCCC patients.

KEYWORDS: cervical tumor, small cell carcinoma, neuroendocrine tumor.

Neuroendocrine carcinoma of the cervix (NECC) is a rare and characteristic primary malignant tumor, with a strong invasive capacity, easy recurrence and early distant metastasis. In 1997, based on the morphological similarity of the tumors, described by American Association of Cancer Research (AACR), the congeneric tumors were divided into 4 categories, i.e., typical carcinoid, atypical carcinoid, large-cell neuroendocrine carcinoma (LCNC) and small cell carcinoma (SCC)[1], among which the SCC is more common than LCNC. Over the past several decades, case reports have been the major form for publishing in the literature. However, rapid development has been achieved in basic research, clinical diagnosis and treatment of these tumors. There has been considerable progress in pathological technology and endless in-depth understanding of the tumors from clinicians and pathologists over the past few years, especially with an increase in analysis and reports related to small cell carcinoma of the cervix (SCCC).

Clinical manifestations

In comparing SCCC with uterine cervix cancer (UCC) of the common types, there is no significant difference between various parameters, such as number of pregnancies, race, socioeconomic status, tumor size, growth pattern, depth of mesenchymal infiltration, as well as clinical stages[2]. Main symptoms of the tumors include irregular colporrhagia or contact bleeding, and some may present with vaginal secretions. No abnormal hormone secretions occurred in most of the patients during the clinical and laboratory examinations. Occasionally there were clinical manifestations of an ectopic hormone syndrome and a paraneoplastic syndrome, such as hypoglycemia, Cushing's, myasthenic and carcinoid syndromes.

Biological behaviour

SCCC has many common features with small cell carcinoma of the lung (SCCL), i.e., frequent lymphatic involvement, vascular infiltration, and occurrence of hematogenous metastasis. In the study of Boruta et al.[3], positive lymph nodes were found in 34 patients with early IB–IIA SCCC. The positive rate of lymph nodes amounted to 52% (15/29 cases) and lymph-node interspaceal involvement to 78% (21/27 cases). Previous reports from China showed that there were positive lymph nodes in 15 of 30 SCCC cases[2,4,5]. Compared to ordinary UCC, SCCC has the characteristics of rapid metastasis at distant organs, with the following organs as the most common sites, i.e. lung, liver, brain, bone, kidney, breast and pancreas, etc. Viswanathan et al.[6] reported that the median survival time of 21 SCCC patients, with positive neuroendocrine antibody, was 38 months, and distant hematogenous metastases were found ante mortem in most of the patients. Therefore, an overall clinical examination should be conducted before treatment of SCCC patients, in order to preclude distant metastasis and to avoid unsuitable therapy.

Pathological features

The definition of SCCC defined by Albores et al.[1] is as follows: the cancer cells are small and round, or spindle-shaped, with little cytoplasm, granular and trachychromatic nuclear chromatin, absent of a nucleolus or just unclear nucleoli. The general features of SCCC are nonspecific and its expression is a polypiform or inward infiltration, usually with a surface ulceration, hemorrhage and necrosis, and a tumor of grey or grayish-yellow color and hard texture. Microscopic characteristics include the following, i.e. ①the tumor is formed mainly by the small and round cells (oat cells) of homologous shape and size, with little cytoplasm, trachychromatic nuclear chromatin, a big nucleoplasmic ratio, free of the nucleolus or just fuzzy nucleoli. Mitoses are common; ②the tumor has an asystematic distribution, or a nest-like formation, bridge-like and funiform arrangement, with frequent extensive necrosis; ③SCCC sometimes exists together with adenocarcinoma or squamous carcinoma, with a small cell ratio of over 60%.

Electron-microscopic features are as follows: neuroendocrine granules can be found in part of the tumor cells, the granulometric texture is pyknotic and the size ranges from 100 to 250 nm. Unified application of various immunohistochemical markers provides the diagnosis, i.e., tumor markers in relation to neuroendocrine cells, such as neuronspecific enolase (NSE), chromogranin (CgA), and positive synaptophysin (Syn). Albores-Saavedra[7] deemed the CD56 (nerve cell adhesion molecule) as the most sensitive, having a positive rate of 88% (22/25 cases).

SCCC is easily misdiagnosed as the following tumors, e.g., poorly differentiated squamous small-cell carcinoma, poorly-differentiated adenocarcinoma with a carcinoid manifestation, non-Hodgkin lymphoma, granular cell sarcoma, small cell melanoma, stromal sarcoma, embryo rhabdomyosarcoma and primitive neuroectodermal tumor[8].

Characteristics of molecular biology

Our review showed that SCCC closely relates to HPV infection. In the study by Wang and Lu[9], the total HPV positive rate was found in 22 cases of SCCC, that of HPV18 in 17 cases, HPV16 in 4, and HPV16 and 18 in 1. As a control, HPV of 9 cases with SCC of the rectum and 8 cases with SCC of the bladder were totally negative. In the study of Masumoto et al.[10], the total positive rate of HPV was seen in the samples of 10 cases with SCCC, that of HPV18 in 9 cases and HPV16 in 1. It was confirmed by an in situ hybridization that integration is the major form for HPV DNA to reside in the nucleus. The report of Wang et al.[11] indicated that in 26 SCCC cases, HPV18 was positive in 17 and HPV16 in only 1. It was thought that, although HPV18 and human gene integration plays a key role in the carcinogenesis of SCCC, it remains unclear how neuroendocrine differentiation has been brought about. It has been confirmed previously that the HPV E7 oncoprotein can inactivate the tumor suppressor proteins p53 and Rb. The Rb protein is degraded owing to a combination between the HPV E7 and the pRb, resulting in a strong expression of the p16 (a cyclin-dependent kinase-blocker protein) and abnormal control of the cell cycle. Based on the report of Wang et al.[9], pRb was not expressed in 18 of the 22 (81.8%) samples of SCCC cases, an overexpression of the p16 was found in 20 cases, and no expression of p53 was detected in 22 cases (100%). Masumoto et al.[10] reported that there was a strong p16 expression in the 10 examined samples. They suggested that the difference between squamous carcinoma of the cervix and SCCC lies in that there is a protein binding of HPV16 E7 with the Rb in squamous carcinoma of the cervix, and in SCCC HPV18 E7 binds the Rb protein, which is possibly the reason for a poor prognosis of SCCC.

Diagnosis

SCCC has a high malignancy, with a rather poor

prognosis and different treatment plan compared to other tumors of the cervix. Therefore, it is very important to distinguish it from other tumors of the cervix.

Diagnosis of SCCC is based on histo-pathomorphology. Light microscopy, immunohistochemical markers and electron-microscopy have been jointly employed to improve the accuracy of the diagnosis. Many SCCC patients have failed to obtain diagnostic results from a cervical desquamated cell smear before a histological diagnosis, so it was suggested that the sensitivity of cervical exfoliative cytodiagnosis for SCCC is low. However, Kim et al.[12] found that the characteristics of tumor cells displayed by the SCCC cell smear is sufficient to conclude the cytodiagnosis. The Papanicolaou smear of 18 SCCC patients was retrospectively reviewed. The results showed that SCCC was cytologically diagnosed or suggested in 14 cases (79%). The features of SCCC were as follows: there was very little cytoplasm in the tumor cells, bold and point-like nuclear chromatin, significant effect of nuclear condensation and smearing, and cell aggregation of various sizes.

Some authors[8,13]have analyzed the characteristics of liquid-based thinlayer cytologic smears for SCCC: small and round tumor cells, existing individually or forming loosened small aggragations (<10 cells, typical major lamellar aggregate could be seen in squamous carcinoma and adenocarcinoma); a high nuclear to cytoplasmic ratio; round or orbicular-ovate cell nucleus, heavy-stained chromatin, an irregular or crimpled nuclear envelop, with an indistinctive nucleolus, and little cytoplasm. Mutual nuclear condensation and cytological autophagia were common in the cell aggregations. The background was an obvious tumor quality, a compounded existence of necrobiotic fragments with isolated small and round cells, apoptotic bodies and nuclear fragments were common, while in the smear of the cases without squamous cell cancer of the cervix, the typical non-squamous feature and rosette formation of the "fruit-salad type" necrosis occurred because of presence of the cell cornification. A report on the characteristics of colposcopic imaging diagnosis was not presented.

SCCC is very easily misdiagnosed as a small-cell and poorly differentiated squamous carcinoma, which is possibly the reason of a quite low incidence of SCCC. The diagnosis can be improved and that incidence can be gradually increased with physician's better understanding of this tumor.

Treatment

Early distant metastasis is prone to occur in SCCC cases, and employment of conventional surgical and radiotherapeutic methods, or joint use of these two methods for treating squamous carcinoma of the cervix, are unsatisfactory. There is even a high death rate in patients with early-stage SCCC. Sheets et al.[14] treated 14 patients with Stage-Ib and IIa SCCC, using a simple surgical operation or adjuvant radiotherapy combined with surgery, among which 12 patients (86%) died within 31 months, with a mean survival rate of only 13.5 months.

Since the chemotherapeutic method has played a key role and has produced satisfactory results in treating SCCC, and the histological appearance and biological behavior of SCCC resembled SCCL, the combined therapy, including chemotherapy plus surgery and/or radiotherapy, is strongly advocated at present. A surgical operation and radiotherapy can be used to remove the local lesion, and chemotherapy employed for controlling the distant metastasis. The chemotherapeutic regimen of SCCC has drawn on experience of the regimen for treating SCCL. The commonly used regimens include VAC, PE and VAC/PE, i.e., VCR+ADM+ CTX, DDP+VP16 or they are traded off for each other.

Chang et al.[15] reported that adjuvant chemotherapy after extensive hysterectomy was conducted with 23 patients having Stage-Ib and II SCCC from the Taiwan Chang Gung Memorial Hospital. During the period from the years 1984 to 1988, the PVB regimen for squamous carcinoma of the cervix (cisplatin+vinc ristine+bleomycin) was employed, with 8 courses of treatment, and after 1988 the VAC/PE regimen was adopted, with 6 courses of treatment. Until the end of follow-up (a median follow-up of 41 months), 10 of the 14 patients (71%) receiving the VAC/PE regimen achieved a tumor-free survival, and only 3 of the 9 patients (33%) receiving the PVB therapy survived. At the same time, these authors have summarized 17 reports including 40 cases, among which 19 of the 28 patients (68%) receiving VAC/PE treatment plan achieved a tumor-free survival, and 4 of the 12 patients (33%) receiving the PVB regimen still survived. The median survival time of the 23 survivors was 47 months. There was a significant difference between the medication groups, and it indicated that treating SCCC using the chemotherapeutic regimen for SCCL is feasible. Although there were some side effects, the therapeutic efficacy was positive.

Boruta et al.[2] reported on 34 early Stage-Ib to IIa patients for whom the treatment plan of surgery plus chemotherapy, with or without radiotherapy, was employed. In the patients, a PE chemotherapeutic regimen was conducted in 15, VAC in 7 and VAC/PE in 2. Other regimens were used in the remaining 10

cases. Radiotherapy was concurrently performed in 20 cases. The results showed that VAC/PE was an effective regime, and there was no difference between the two, though the chemotherapeutic reaction of the PE regime could be more palliative. There was no difference whether or not adjuvant radiotherapy was added.

On the premise that combination therapy with paclitaxel and carboplatin for SCCL has attained good results, trials of the regimens for treating SCCC have been performed in some hospitals. During the years 1998-2002, Hoskins et al.[16] randomly divided 31 SCCC patients from the Columbia Cancer Center, UK, into two groups. The patients from both groups received conventional pelvic field radiotherapy, abdominal para-aortic field irradiation and the PE regimen. One of the groups was also treated with a combined regimen composed of paclitaxel and carboplatin. Analytic of the results indicated the paclitaxel treatment failed to enhance the curative effect, however it could obviously minimize the side effects. Other reports have shown that there is a satisfactory reaction following adjuvant chemotherapy of SCCC[17].

Prognostic factors

The prognosis of SCCC is poor. The 5-year survival of the Stage-I patients is 30%. The factors affecting prognosis of SCCC include the stages and tumor size, extent of tumor involvement in the cervix and also the presented vascular infiltration. A report by Chang et al.[15] indicated that in 10 of 34 SCCC cases with a tumor diameter of less than 2 cm, the median survival time (MST) was 155 months, while in the remaining 24 cases, with a tumor diameter of over 2 cm, the MST was only 14 months. The MST of the early stage-SCCC patients, i.e., Stage-I to IIA, was 31 months, and that of the late stage patients, i.e., Stage-IIB to IVB, 10 months. At the same time they found that the prognosis of the patients who smoke was poor, possibly because smoking was related with HPV infection. Prognosis of the patients with a mixed histological type was better than those with a simple histological type. Age, race, amenorrhea and hormone replacement therapy were not included in the prognostic factors. They suggested that lymphatic metastasis and vascular infiltration did not affect the prognosis. Most authors[3,18] consider lymph node metastasis to have a major effect on the prognosis. Analysis by Boruta et al.[2] indicated that in 34 early Stage-Ib to IIa patients, 20% of the patients with positive lymph nodes survived at the end of the follow-up (the median follow-up period was 14 months), and the survivors with negative lymph nodes amounted to 64%. Tangjitgamol et al.[19] reported that in 24 cases with SCCC, 95.8% of the cases were VEGF positive, and 41.7% (10/24) HER-2/neu positive. The SCCC patients with a negative HER-2/neu and positive VEGF had a poor prognosis.

In conclusion, more attention has been increasingly paid to SCCC owing to its high malignancy and poor prognosis, though it is a rare gynecologic neoplasm. Our retrospective analysis suggests that postoperative adjuvant chemotherapy may improve prognosis of the patients. However, a prospective case control study is yet lacking, and accumulation of more data to seek optimal treatment plan is expected.

REFERENCES

1 Albores SJ, Gersell D, Gilks CB, et al. Terminology of endocrine tumors of the uterine cervix: results of a workshop sponsored by the College of American Pathologists and the National Cancer Institute. Arch Pathol Lab Med 1997; 121: 34-39.
2 Jiang Z, Pei H, Qu Y. Clinical analysis of 12 cases with small cell carcinoma of the cervix. J Oncol 2005; 11: 261-262.
3 Boruta DM, Schorge JO, Duska LA, et al. Multimodality therapy in early-stage neuroendocrine carcinoma of the uterine cervix. Gynecol Oncol 2001; 81: 82-87.
4 Shu KY, Ai XY, Li LY, et al. Clinical pathological analysis of 24 cases with small cell carcinoma of the cervix. Prac Clin Med 2005; 6: 64-67.
5 Tang L, Sheng XG, Li DP, et al. Clinical report of 3 cases with small cell carcinoma of the cervix. Chin J Clin Oncol 2004; 31: 114-115.
6 Viswanathan AN, Deavers MT, Jhingran A, et al. Small cell neuroendocrine carcinoma of the cervix: outcome and patterns of recurrence. Gynecol Oncol 2004; 93: 27-33.
7 Albores-Saavedra J, Latif S, Carrick KS, et al. CD56 reactivity in small cell carcinoma of the uterine cervix. Int J Gynecol Pathol 2005; 24: 113-117.
8 Ng WK, Cheung LK, Li AS, et al. Thin-layer cytology findings of small cell carcinoma of the lower female genital tract. Review of three cases with molecular analysis. Acta Cytol 2003; 47: 56-64.
9 Wang HL, Lu DW. Detection of human papillomavirus DNA and expression of p16, Rb, and p53 proteins in small cell carcinomas of the uterine cervix. Am J Surg Pathol 2004; 28: 901-908.
10 Masumoto N, Fujii T, Ishikawa M, et al. P16 overexpression and human papillomavirus Infection in small cell carclnoma of the uterine cervix. Hum Pathol 2003; 34: 778-783.
11 Wang KL, Yang YC, Wang TY, et al. Neuroendocrine carcinoma of the uterine cervix: A clinicopathologic retrospective study of 31 cases with prognostic implications. J Chemother 2006; 18: 209-216.
12 Kim Y, Ha HJ, Kim JS, et al. Significance of cytologic smears in the diagnosis of small cell carcinoma of the uterine cervix. Acta Cytol 2002; 46: 637-644.
13 Khunamornpong S, Siriaunkgul S, Suprasert P. Cytology of small cell carcinoma of the uterine cervix in serous effusion: a report on two cases. Diagn Cytopathol 2001; 24: 253-255.
14 Sheets EE, Berman ML, Hrountas CK, et al. Surgically treated, early-stage neuroendocrine small-cell cervical carcinoma. Obstet Gynecol 1988; 71: 10-14.

15 Chang TC, Lai CH, Tseng CJ, et al. Prognostic factors in surgically treated small cell cervical carcinoma followed by adjuvant chemotherapy. Cancer 1998; 83: 712-718.
16 Hoskins PJ, Swenerton KD, Pike JA, et al. Small-cell carcinoma of the cervix: fourteen years of experience at a single institution using a combined-modality regimen of involved-field irradiation and platinum-based combination chemotherapy. J Clin Oncol 2003; 21: 3495-3501.
17 Bermudez A, Vighi S, Garcia A, et al. Neuroendocrine cervical carcinoma: a diagnostic and therapeutic challenge. Gynecol Oncol 2001; 82: 32-39.
18 Chan JK, Loizzi V, Burger RA, et al. Prognostic factors in neuroendocrine small cell cervical carcinoma: a multivariate analysis. Cancer 2003; 97: 568-574.
19 Tangjitgamol S, Ramirez PT, Sun CC, et al. Expression of HER-2/neu, epidermal growth factor receptor, vascular endothelial growth factor, cyclooxygenase-2, estrogen receptor, and progesterone receptor in small cell and large cell neuroendocrine carcinoma of the uterine cervix: a clinicopathologic and prognostic study. Int J Gynecol Cancer 2005; 15: 646-656.

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47 Bottoni A, Piccin D, Tagliati F, et al. MiR-15a and miR-16-1 down-regulation in pituitary adenomas. J Cell Physiol 2005; 204: 280-5.
48 Futreal PA, Coin L, Marshall M, et al. A census of human cancer genes. Nat Rev Cancer 2004; 4: 177-83.
49 Carninci P, Kasukawa T, Katayama S, et al. The transcriptional landscape of the mammalian genome. Science 2005; 309: 1559-63.
50 Griffiths-Jones S. The microRNA Registry. Nucleic Acids Res 2004; 32: D109-D111.
51 Zhu S, Si ML, Wu H, et al. MicroRNA-21 targets the tumor suppressor gene tropomyosin 1 (TPM1). J Biol Chem 2007; 282: 14328-14336.