Presentation of a patient with pT2bN1M0 small cell carcinoma of the uterine cervix who obtained long-term survival with maintenance chemotherapy, and literature-based discussion

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Summary

Background: Small cell carcinoma of the uterine cervix is a rare cervical carcinoma that advances early and is associated with a poor prognosis. We present a case of this disease which invaded the parametrium and metastasized to the pelvic lymph node. The patient underwent postoperative concurrent chemoradiotherapy (CCRT) followed by maintenance chemotherapy and obtained long-term survival. *Case:* A 26-year-old patient, who had conceived on two occasions without giving birth and had smoked for ten years, underwent radical hysterectomy with a diagnosis of Stage Ib1 cervical carcinoma in December 2006. The patient showed parametrial invasion, and metastasis to the left external iliac node and vaginal stump. With a diagnosis of pT2bN1M0, the patient underwent CCRT with weekly nedaplatin as postoperative therapy. For the maintenance chemotherapy, from May 2007, ten courses of PE therapy (CDDP, 15 mg/body; VP-16, 100 mg/body × 3) were performed. No recurrent signs have been observed for 39 months after the first operation. *Conclusion:* PE therapy may be useful as maintenance therapy, although there are no established treatments for small cell carcinoma of the uterine cervix.

Key words: Small cell carcinoma of the uterine cervix; Maintenance chemotherapy; Combination of CDDP and VP-16; Poor prognosis.

Introduction

Small cell carcinoma of the uterine cervix is a rare cervical carcinoma that advances early and is associated with a poor prognosis [1]. Due to the small number of cases, treatment strategies have not yet been established. We experienced one case of small cell carcinoma of the uterine cervix, who underwent postoperative concurrent chemoradiotherapy (CCRT) followed by maintenance chemotherapy because of parametrial invasion and pelvic lymph node metastasis, and obtained a long-term survival. We present this case together with a literature-based discussion.

Case Report

The patient was 26 years old, had conceived on two occasions without giving birth, had smoked since the age of 16, and her height and weight were 150 cm and 51 kg, respectively. The patient had been aware of her atypical genital bleeding since the spring of 2006. When visiting her former doctor in November 2006, the patient showed a thumb-tip-size tumor mass on the anterior lip of the vaginal portion of the uterine cervix. A cytodiagnosis was performed, and as the mass was suspected to be squamous cell carcinoma. The patient was referred to the authors' department for close investigation and treatment of the cervical lesion. There was no noteworthy medical history. Pelvic examination found the uterus to be normal-sized and a thumb-tip-sized hemorrhagic tumor mass on the anterior lip of the vaginal portion of the uterine cervix. The patient was diagnosed with Stage Ib1 cervical carcinoma because of no invasion in the bilateral parametrium. Neither peripheral blood nor biochemical tests showed abnormalities. Tumor marker tests were as follows: SCC, 1.3 ng/ml; CEA, 1.3 ng/ml; CA125, 11.5 U/ml; neuron specific enolase (NSE), 8.4 ng/ml (normal range: 0 to 12.0 ng/ml); and pro-gastrin-related peptide, 22.4 pg/ml (normal range: 0 to 46.0 pg/ml). The cytodiagnosis of the uterine cervix revealed high-N/C small ovoid cells aligned in an Indian file as well as pair cells (Figure 1). The cytodiagnosis suggested small cell carcinoma. Histopathology diagnosis of the cervical tumor revealed that high-N/C small tumor cells with poor cytoplasm had proliferated to form a solid mass. Thus, the patient was diagnosed with small cell carcinoma. Positron emission tomography (PET)-CT showed accumulation of 18F-fluorodeoxyglucose in the cervical tumor and the left external iliac lymph nodes.

The patient underwent radical hysterectomy, bilateral salpingo-oophorectomy, pelvic lymphadenectomy, and paraaortic lymph node biopsy with a diagnosis of Stage Ib1 cervical carcinoma in December 2006. Figure 2 shows the removed specimens. Postoperative histopathology diagnosis, like the preoperative biopsy, revealed that high-N/C small tumor cells with poor cytoplasm had proliferated to form a solid mass (Figure 3A). There was also marked invasion to the lymphatic vessels. On immunostaining, NSE and Grimelius stains were positive, while chromogranin A was negative, and cytokeratin was negative. From these findings, the patient was finally diagnosed with small cell carcinoma of the uterine cervix. The small cell carcinoma had metastasized to the left external iliac nodes, the left cardinal ligament, and the vaginal stump (Figure 3B-D). With a diagnosis of pT2bN1M0, the patient underwent CCRT as a postoperative therapy. For the radiotherapy, a total of 45 Gy radia-

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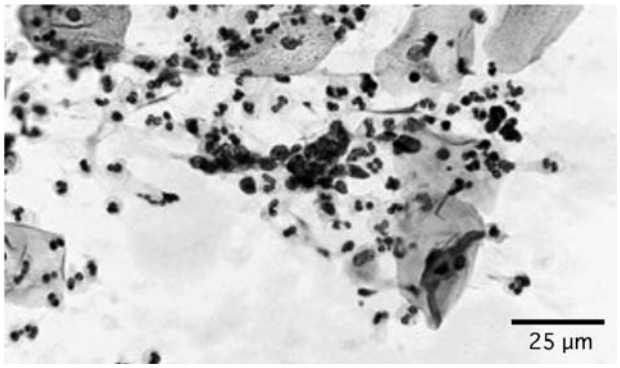

Figure 1. — Cytological finding gathered from small cell carcinoma of the uterine cervix. The cytodiagnosis of the uterine cervix revealed high-N/C small ovoid cells aligned in an Indian file as well as pair cells.

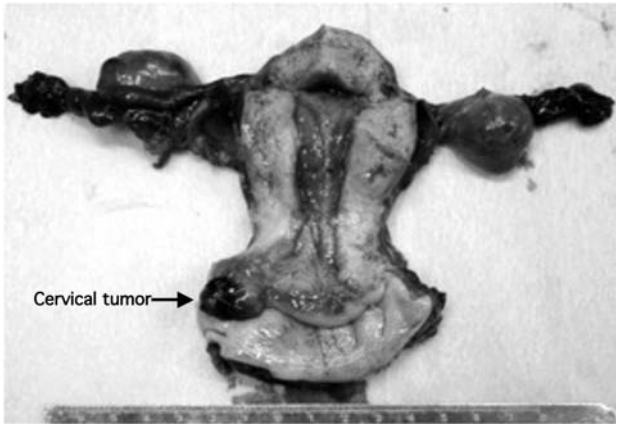

Figure 2. — Macroscopic picture of the removed specimens.

tion was delivered to the whole pelvis and paraaortic regions, and also three fractions of 18 Gy radiation (6 Gy × 3 times) were delivered to the vaginal stump. For the chemotherapy, once-weekly administration of 30 mg/m^2 nedaplatin was performed a total of six times. For the maintenance chemotherapy, from May 2007 ten courses of PE therapy (CDDP, 15 mg/body; VP-16, 100 mg/body × 3) were performed, consisting of three 4-week courses followed by seven 3-month courses. No recurrent signs have been observed for 39 months after the first operation.

Discussion

Small cell carcinoma of the uterine cervix is a rare disease accounting for 0.5 to 6% of the malignant tumors of the uterine cervix [1], and is known as a carcinoma that advances early and is associated with a poor prognosis. Atypical genital bleeding is often observed as a symptom [2, 3]. In some case reports, this carcinoma was observed in patients aged from 33 to 46, tending to occur in young people, compared with usual cervical carcinomas; in other case reports, it developed in patients aged from 22 to 26 [1-7]. Reported causes include association with HPV18, deletion of the short arm of chromosome 3, deletion of the chromosome 9p21 region, and deletion of the p53 gene [1, 2].

Cytodiagnosis of the uterine cervix is generally considered difficult because of the small cells and their low atypism [1, 3]. In fact, this case was diagnosed with small squamous cell carcinoma at first. Cytodiagnosis of small cell carcinoma requires carrying out screening while considering small cell carcinoma. However, this is considered to be difficult because of the small nuclei. In recent years, cytodiagnosis with liquid specimens has become widespread, and immunostaining and other techniques using liquid specimens may increase diagnostic precision.

Concerning tumor marker tests, NSE is generally positive in two-thirds of the cases [8], while SCC, CEA, and SLX are known to be positive at the rate of 30% or less. In the present case, NSE was negative. However, NSE is known to become positive at recurrence, which makes NSE important as a recurrence marker. In cases with no significant tumor markers, PET-CT testing, which enables systemic scanning, may be very effective.

Immunostaining is a useful histopathology diagnosis [2, 9]. According to some reports, NSE and Chromogranin A stainings are positive in 70-88% and 40 -50%, respectively. In addition, Grimelius and CD56 stainings are also useful as immunostaining, and Virswanathan *et al*. [4] reported that chromogranin, synaptophysin, and CD56 stainings were positive in 31.4%, 37.6%, and 29.4% of 51 patients with small cell carcinoma or neuroendocrine carcinoma, respectively.

Small cell carcinoma of the uterine cervix is known to advance early and to cause early distant metastasis; pelvic lymph node metastasis is observed at diagnosis in many patients, and occurs generally at a rate of 40-86% [10]. Sheets *et al*. [11] report that pelvic lymph node metastasis and vasculature invasion were observed in eight (57%) and seven (50%) of the 14 operated patients with small cell carcinoma of the uterine cervix, respectively.

Small cell carcinoma of the uterine cervix is associated with a poor prognosis. Recurrence is generally seen in 80% of cases within 8-16 months after diagnosis, and is also often observed in non-irradiated fields [4, 6]. The five-year survival rate ranges generally from 17-67% for all extensive stages, but was reported to be 0% in patients showing FIGO Stage II or higher or positive pelvic lymph node metastasis [4, 5, 12-14].

Standard therapy for small cell carcinoma of the uterine cervix has not yet been established because it has not been examined in large case groups [5-7, 13]. According to the literature, early-stage small cell carcinoma of the uterine cervix should be treated by surgery followed by chemotherapy or CCRT [7, 13, 15]. Regarding the procedure of hysterectomy, Sevin *et al*. [16] report radical hysterectomy to be desirable. However, Kasamatsu *et al*. [17] describe that although providing benefits for patients who show shallow cervical stromal invasion without pelvic lymph node metastasis, radical hysterectomy is less useful for other patients. Bifulco *et al*. [18] emphasize that postoperative chemotherapy should be carried out in such a way that it has a greater effect than operative procedures. Many reports show that VAC (vincristine, doxorubicin, and cyclophosphamide) or PE (CDDP, VP-16) are

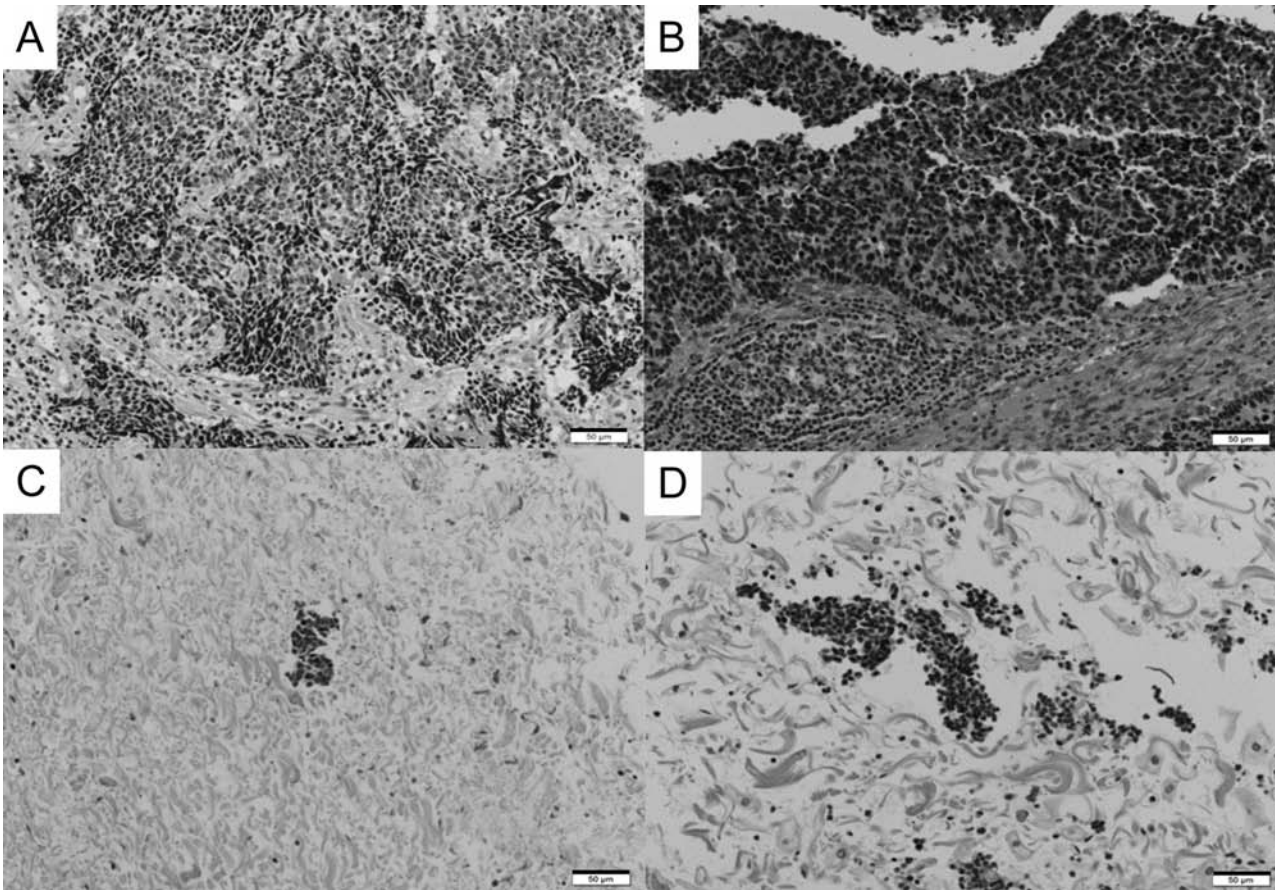

Figure 3. — Microscopic findings observed from the removed specimens. A) histopathology of the cervical tumor revealed that high-N/C small tumor cells with poor cytoplasm had proliferated to form solid mass. B) the small cell carcinoma had metastasized to the left external iliac nodes. C) the small cell carcinoma had invaded to the left cardinal ligament. D) the small cell carcinoma had invaded to the vaginal stump.

efficacious as chemotherapy for small cell carcinoma of the uterine cervix, and many literature reports refer to regimens for small cell lung carcinoma [3, 5]. Hoskins *et al*. [15] performed a historical control study to examine the efficacy of CCRT in 31 cases of small cell carcinoma. The first group of 17 patients had undergone PE and whole-pelvis irradiation, and some had received additional irradiation to the paraaortic lymph nodes. The second group of 14 patients had further undergone TC therapy and irradiation to the paraaortic lymph nodes. There were no significant differences in the therapeutic effect between the first and second protocols. With both protocols, however, the three-year survival rate for CCRT was 60%, which was higher than any previously reported value. Lee *et al*. [7], in their report on early-stage, or Ib-IIa, small cell carcinoma of the uterine cervix, describe that between post-operative-chemotherapy and CCRT groups there were no significant differences in the five-year survival rate (52% vs 45.5%, $p = 0.37$) or in patient backgrounds, concluding that CCRT cannot lead to improvement in prognosis.

Lee *et al*. [7] reported that a neoadjuvant-chemotherapy (NAC) group had poorer prognosis than a non-NAC group, suggesting that neoadjuvant chemotherapy may need to be carefully selected. On the other hand, Bermudes *et al*. [19] reported that they found 50% or more tumor regression in 84.7% of bulky-disease patients treated with three courses of PVB (cisplatin, vincristine, and bleomycin) as NAC, and observed their survival time to change with post-NAC tumor diameter. This suggests that if chemotherapy with a high response rate is established, NAC should be examined for efficacy.

We decided to treat the present case with CCRT after radical hysterectomy. Although TC, VAC, PE, and other drugs were considered for use in combination with the radiotherapy, nedaplatin was selected in order to reduce side-effects. It was decided to perform PE therapy as maintenance chemotherapy because a randomized study on small cell lung carcinoma showed the response rate of PE therapy to be 78% [20]. Since there are no reports examining maintenance chemotherapy for small cell carcinoma of the uterine cervix, only the previously-examined maintenance chemotherapy for small cell lung carcinoma served as a reference, and the usefulness of maintenance chemotherapy has not yet been established. However, Hanna *et al*. [21] reported on the usefulness of maintenance chemotherapy: 4-time treatment with etoposide, ifosfamide, and cisplatin, and subsequent three-month oral administration of etoposide resulted in exten-

sion of the recurrence-free survival time in patients with small cell lung carcinoma. Thus, it was planned to apply PE therapy as maintenance chemotherapy in the present case, a high-risk patient showing parametrial invasion and pelvic lymph node metastasis. It has been reported that the three-year survival rate is 0% in patients with Stage IIb or higher small cell carcinoma of the uterine cervix [13]. Considering that we have observed no recurrence in the present case, PE therapy may become regarded as useful maintenance chemotherapy, but could not be suggested by only the results of the present case.

Concerning prognostic factors of small cell carcinoma of the uterine cervix, Chan *et al*. [13] carried out a multivariate analysis of prognostic factors in 23 cases of small cell carcinoma of the uterine cervix, and found smoking and clinical extensive stage to be independent significant poor-prognosis factors. In particular, they reported smoking to be a poor-prognosis factor in Stage I-IIa, cases. The present case was a smoker, and this needs to be pointed out. Boruta 2nd *et al*. [3] report pelvic lymph node metastasis to be a significant poor-prognosis factors. Hoskins *et al*. [15] regard not only clinical extensive stage but image-based extensive stage to be the unique prognostic factor. This may be because many patients diagnosed with FIGO Stage I-II small cell carcinomas of the uterine cervix have already had paraaortic lymph node metastasis or distant metastasis. Lee *et al*. [7] report FIGO stage to be a unique poor-prognosis factor. Thus, only the FIGO stage can be considered a definite poor-prognosis factor, however, further examination may be necessary in the future. The present case has lived with no disease for 39 months, although is expected to have a very poor prognosis due to her postoperative extensive Stage of IIb, positive pelvic lymph node metastasis, and smoking history.

Small cell carcinoma of the uterine cervix is a rare cervical carcinoma that is associated with a poor prognosis. While the rareness of this carcinoma makes it difficult to plan clinical studies, it is desirable that a standard therapy be established. It is important to separate small cell carcinoma of the uterine cervix from other cervical carcinomas, and to establish more efficacious therapy for this carcinoma. We believe that there is a need to firstly bring together cases of small cell carcinoma of the uterine cervix on a national level, and to examine these cases in a retrospective manner.

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